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METABOLISM STUDIES IN INFANTS SUFFERING FROM CHRONIC NUTRITIONAL DISTURBANCES (ATHREPSIA) *

KIRSTEN UTHEIM, M.D.
ST. LOUIS

Since the establishment of pediatrics as an independent branch of medicine, there has been a great deal of discussion as to the pathogenesis of the chronic nutritional disturbances of infancy. The discussion has, for the greater part, taken place in the German literature. Many types of disturbance, among them those which we now know to be due to such chronic infections as tuberculosis and syphilis, have been included by some authors in the discussion.

This paper deals with that chronic condition of extreme malnutrition of infants which occurs independently of known infection and is not accompanied by acute gastro-intestinal or nervous symptoms. Without entering into any extensive discussion of the symptomatology or nomenclature, suffice it to say that the condition is, in a general way, the one which has been described by the terms "infantile atrophy," "marasmus" or "alimentary decomposition." On account of the fact that some of these terms, particularly the one "marasmus," have been used to include such a large variety of unrelated conditions, whereas we are really dealing with a clinical entity, it has been suggested by Marriott that the term athrepsia originally introduced by Parrot [1] in his extensive monograph on the subject is the preferable term.

One of the earlier theories of athrepsia considered the condition as the result of an actual atrophy of the intestinal tract. Heubner's [2] complete anatomic examinations of the intestinal tract made it clear, however, that such changes as have been earlier described were not pathological but were present even in the normal intestinal tract and were merely due to post mortem changes.

The enzymes in the intestinal tract were studied by Rosenstern [3] and Reeve-Ramsay; [4] both found that pepsin secretion was diminished in athreptic infants.

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*From the St. Louis Children's Hospital and the Department of Pediatrics, Washington University School of Medicine.

1. Parrot: L'Athrepsie, Paris, 1877.
2. Heubner: Jahrb. f. Kinderh. **53**:35, 1901.
3. Rosenstern: Berl. klin. Wchnschr. **1**:542, 1908.
4. Reeve-Ramsey: Jahrb. f. Kinderh. **68**:191, 1908.

Heubner [2] propounded a theory of the pathogenesis of athrepsia from the standpoint of the energy balance. Based on a metabolism experiment on an athreptic infant, he came to the conclusion that a negative energy balance occurred on account of lack of absorption from the intestinal tract, in other words, that there was a partial inanition as a result of absorption of an insufficient amount of food.

Czerny looks on the condition from an entirely different point of view. He assumes that these infants have a low assimilative power for fat and as a result that fatty acids are formed in excess in the intestinal tract. These fatty acids, according to Czerny, require alkali for neutralization and this alkali is taken from the tissues and secreted into the gastro-intestinal tract. In the presence of diarrhea it is, according to Czerny, the sodium and potassium which is thus secreted and lost; and in the presence of constipation with soap stools, the calcium salts. In order to make up for the alkali deficit caused in this manner, ammonia is formed in the body and excreted in the urine. According to this theory, the essential factor in the pathogenesis of the disturbance is the condition of demineralization of the body. On account of this mineral loss it is assumed that the cell structure and tissue composition is altered and that if a sufficient loss takes place the normal cell function will be so disturbed that a building up of new tissue is impossible even if the processes in the intestinal tract are restored to normal. Czerny's theory is based on the experimental work of Keller and of Steinitz. In 1897 Keller [5] examined eleven infants suffering from acute and chronic gastro-intestinal disturbance and found in all except one a considerably increased ammonia excretion in the urine. He came to no conclusion as to whether this high ammonia excretion was due to an increase of acids in the body or to an impairment of the function of the liver for the synthesis of urea. In a later work Keller [6] attempts to show that there is no disturbance of liver function. The other work on which Czerny's theory is based was done by Steinitz [7] in 1903. He found that a large amount of fat in the feeding increased the ammonia output in the urine.

The theory of Czerny and Keller has met considerable opposition. Pfaundler [8] was one of the first to criticise it. He found an increased ammonia output in the urine of athreptic infants but never as much as was found by Keller. Pfaundler examined the oxidizing power of the liver of these infants post mortem, and made observations which led him to believe that there occurred a degeneration of liver tissue with resulting lack of power to synthesise ammonia to urea. Pfaundler considers the disturbance in the intestinal tract as merely secondary

5. Keller: Jahrb. f. Kinderh. **44**:25, 1897.
6. Keller: Jahrb. f. Kinderh. **48**:397, 1898.
7. Steinitz: Jahrb. f. Kinderh. **57**:689, 1903.
8. Pfaundler: Jahrb. f. Kinderh. **54**:247, 1901.

to primary disturbances in the body cells which profoundly affect the intermediary metabolism. In 1906 Meyer and Langstein [9] stated, without giving the exact figures, that they had never found an increased ammonia output in the urine of athreptic infants and denied that acidosis played any rôle in the development of the condition.[10] In 1910 L. F. Meyer [11] found a negative salt balance in infants suffering from "dyspepsia" and "dekomposition" and receiving a diet low in fat. Jundell [12] found a perfectly normal metabolism in an infant suffering from "dyspepsia" and concludes that the pathologic process in this condition is a local one limited to the intestinal tract.

Marriott [13] considers athrepsia as the result of a prolonged period during which food absorption and utilization is less than the caloric output, or, in other words, the result of a prolonged negative energy balance. He emphasizes that once the condition is established there is a diminution in the volume and in the volume flow of the blood which results in the inability of the infant to utilize suitable food given in reasonable amounts. He considers the slight degree of acidosis sometimes observed as a result but in no way a cause of the condition.

EXPERIMENTAL PART

This work was undertaken in order to determine what changes may take place in the intermediary metabolism of infants suffering from athrepsia. To avoid misunderstanding, it should be stated that all the infants studied as examples of athrepsia were those who for a prolonged period had shown little or no gain in weight and presented the picture of weakness and advanced emaciation without any evident cause for this condition and without general symptoms referable to the central nervous system. Infants with acute gastro-intestinal symptoms are not included in this classification. Wassermann and tuberculin tests were done on every infant in order to exclude those suffering from latent syphilitic or tuberculous infections.

Within the past year this same type of infant was studied in this clinic, especially in relation to the changes occurring in the circulatory system (Marriott,[13] Utheim [14]), and it was found that all infants suffering from the conditions mentioned showed a considerably diminished flow of the blood in the peripheral parts of the body. A close relationship was observed between the nutritional condition of the infant and the degree of impairment of the circulation. Whatever

9. Meyer and Langstein: Jahrb. f. Kinderh. **63**:30, 1906.
10. Die Atrophie an sich hat mit irgendwelcher Acidosis nicht das geringste zu tun.
11. L. F. Meyer: Jahrb. f. Kinderh. **71**:379, 1910.
12. Jundell: Ztschr. f. Kinderh. **8**:235, 1913.
13. Marriott: Am. J. Dis. Child. **20**:461 (Dec.) 1920.
14. Utheim: Am. J. Dis. Child. **20**:366 (Nov.) 1920.

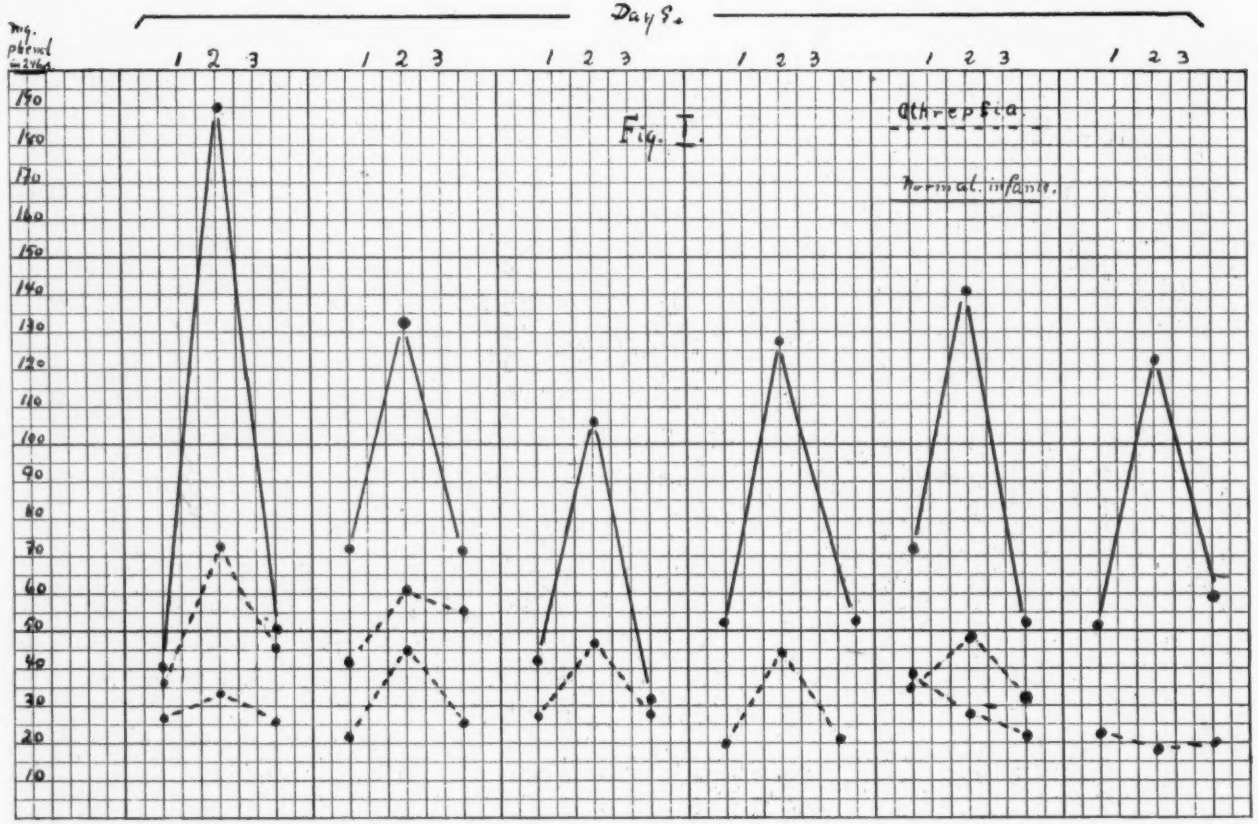

Fig. 1.

Fig. 1.—Showing excretion of phenols in the urines of infants following the administration of 0.5 gm. benzol by mouth. Each line represents an experiment on one infant. The first dot fore period; the second dot period following benzol administration; third dot, after period. Solid lines represent results from normal infants, the broken ones those from athreptic infants.

the cause of this poor circulation, it would naturally tend to lower the oxidizing power of the tissues and render the metabolism incomplete.

OXIDATIVE FUNCTION OF THE BODY IN ATHREPSIA

In order to get some idea of the oxidizing power of the body, the ability of these infants to oxidize benzol to phenol was measured. According to Nencki and Giacosa,[15] benzol is oxidized in the body of normal individuals to phenol, pyrocatechin and hydroquinone which compounds are excreted in the urine, usually in combination with sulphuric acid. Benzol is also oxidized to phenols outside of the body providing conditions are such that nascent oxygen is present (Leeds,[16] Hoppe-Sepler,[17] Nencki and Sieber,[18] Radziszewski.[19]) Nencki and Sieber [20] have stated that normal adults tested at different periods excreted constant amounts of phenol after the administration of a definite amount of benzol. They showed that in such diseases as leukemia and pseudo hypertrophic muscular dystrophy the excretion of phenol was somewhat diminished. Simanowski and Schaumoff [21] found a diminished excretion of phenol in alcohol intoxication. The same authors also determined in animal experiments that an insufficient oxygen intake produced by mechanical pressure on the trachea until dyspnoea was produced led to a decreased oxidation of benzol to one-third of the normal amount. In 1902 Freund [22] administered benzol to two athreptic infants and found less phenol excreted in the urine than in the case of normal infants.

My own observations were made on fifteen infants. Six of the infants were in fairly good nutritional condition, the remaining nine were all athreptic. Each infant was examined for a period of seventy-two hours. The total phenol was determined by Folin's [23] method. During the first twenty-four hours the normal phenol output in the urine was determined. At the beginning of the second twenty-four hour period 0.5 gm. benzol were administered by mouth. During the third twenty-four hour period no benzol was administered. The experiment was discontinued in every instance in which vomiting occurred. The results appear in Table 1 and are shown graphically in Figure 1.

It will be seen from Table 1 that normal and athreptic infants react very differently to the administration of benzol. The increase in phenol

15. Nencki and Giacosa: Ztschr. f. physiol. Chem. **4**:325, 1880.
16. Leeds: Quoted from Nencki and Sieber.[20]
17. Hoppe-Seyler: Quoted from Nencki and Sieber.[20]
18. Nencki and Sieber: Quoted from Nencki and Sieber.[20]
19. Radziszewski: Quoted from Nencki and Sieber.[20]
20. Nencki and Sieber: Arch. f. Physiol. **31**:319, 1883.
21. Simanowski and Schaumoff: Arch. f. Physiol. **33**:251, 1884.
22. Freund: Verhandl. der Gesells. f. Kinderh. **18**:187, 1901.
23. Folin and Denis: J. Biol. Chem. **22**:305, 1915.

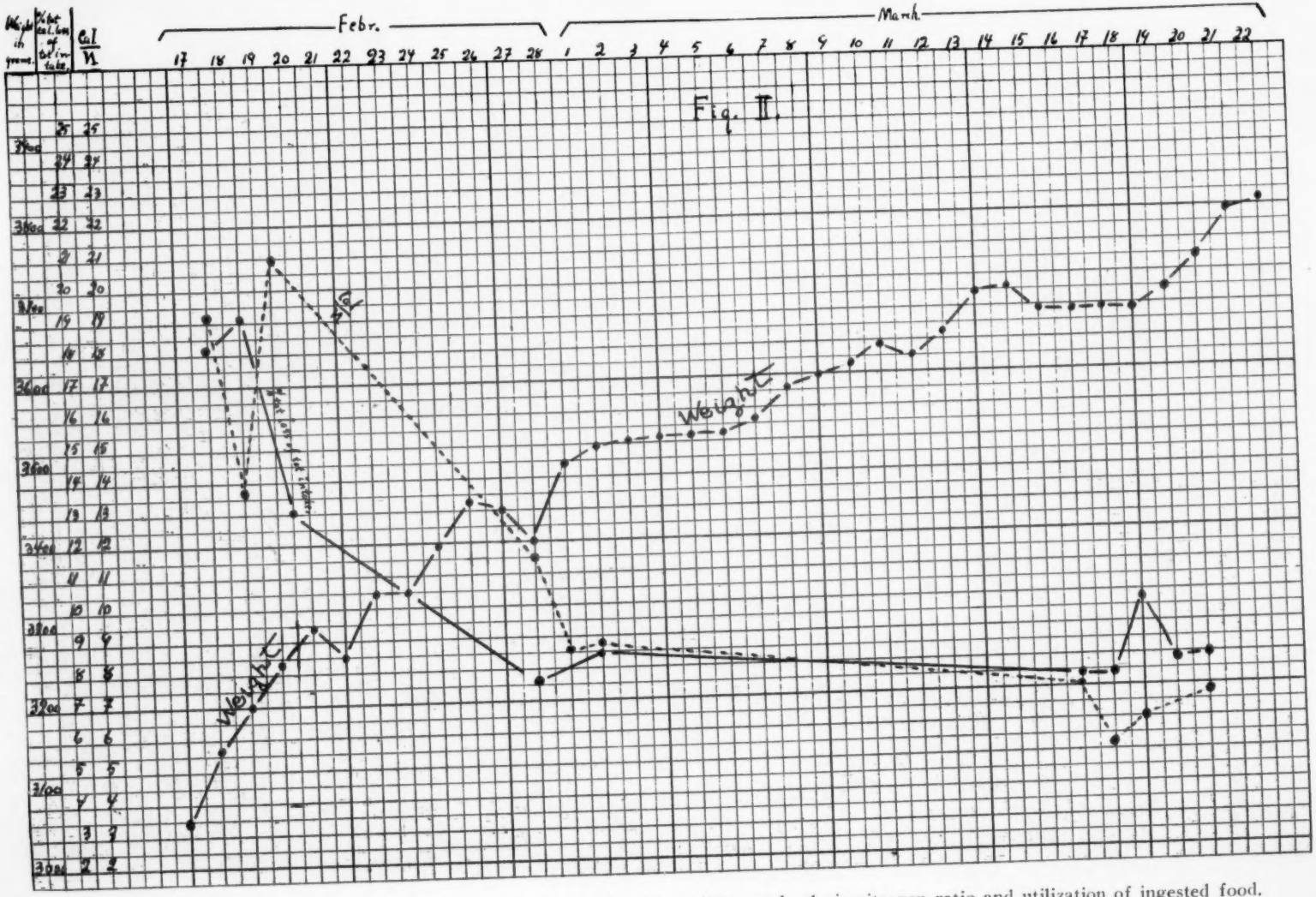

Fig. 2.—This chart shows the relationship between the nutritional condition and caloric nitrogen ratio and utilization of ingested food.

output after administration of benzol to the normal infants was from 60 to 155 mg. whereas in the athreptic infants it did not exceed 36 mg. in the tyenty-four hours. The objection which may be made is that the low phenol excretion is due simply to the poor absorption of the benzol given by mouth. In order to determine if this were the case, the stools from both normal and athreptic infants have been examined after the administration of benzol by mouth and in no instance was any benzol found (method of Allen [24]). It seems, therefore, that one is justified in stating that the tissues of infants suffering from an advanced chronic nutritional disorder are incapable of oxidizing benzol to phenol.

CALORIC-NITROGEN AND CARBON-NITROGEN RATIOS

The next step was to determine if there was any evidence that such decreased oxidation resulted in metabolic disturbances. It was thought

TABLE 1.—PHENOL EXCRETION AFTER 0.5 GM. BENZOL INTAKE ON SECOND DAY

No.	Diagnosis	Weight	Age, Mos.	Mg. Total Phenol Excretion in 24 Hours			Mg. Free Phenol Excreted in 24 Hours		
				First Day	Second Day	Third Day	First Day	Second Day	Third Day
1	Athrepsia	2,050	2	28.7	33.5	25.0	11.9	14.3	12.0
2	Athrepsia	4,200	2½	38.7	74.3	47.0	31.8	59.2	35.1
3	Athrepsia	3,870	8	40.85	61.09	55.7	17.7	28.7	43.2
4	Athrepsia	2,800	2	21.3	45.9	25.07	9.9	22.2	14.8
5	Athrepsia	2,700	2½	27.2	47.9	30.0	15.2	19.0	14.2
6	Athrepsia	2,800	2½	21.0	46.8	22.0	13.6	30.4	15.0
7	Athrepsia	5,550	18	35.65	49.0	22.0	21.9	23.0	20.0
8	Athrepsia	3,100	6	38.2	29.4	21.3	20.4	20.3	13.0
9	Athrepsia	2,500	1½	21.77	17.8	21.5	13.0	10.3	14.5
10	Normal baby	7,900	7	36.0	191.2	50.0	28.0	76.0	25.0
11	Normal baby	4,850	3½	73.5	132.4	71.3	42.1	43 5	37.6
12	Normal baby	4,850	3½	40.4	105.8	30.0	26.7	105.8	25.0
13	Tuberculosis (nutrition good)	6,200	10	54.3	129.7	54.8	24.0	51.6	18.2
14	Convalescent from acute diarrhea	5,850	10	72.0	140.1	52.4	72.0	108.7	47.6
15	Recovered athrepsia	4,450	8	51.0	123.9	59.9	33.1	83.2	51.3

that by examining the energy factors of the urine we would gain an insight into the metabolism of these infants and especially by determining the energy factors in relation to the nitrogen content, or, in other words, what has generally been referred to as the carbon-nitrogen ratio and the caloric-nitrogen ratio which will be referred to hereafter as $\frac{C}{N}$ and $\frac{Cal}{N}$ respectively. The $\frac{C}{N}$ ratio has been studied more than the $\frac{Cal}{N}$ ratio, but as the two are always approximately proportional in different urines they are of equal significance. Two important constituents of normal urine, urea and ammonia, give carbon nitrogen ratios of 0.43 and 0 respectively and tend to keep the ratio in the total urine low. Uric acid, creatinin, amino acids and other organic compounds in normal urine raise the ratios. As the result of a disordered metabolism there were conceivably, therefore, present in the urine

24. Allen: Commercial Chemistry **3**:205.

products which contained considerable amounts of carbon and relatively small amounts, if any, nitrogen. The most important of these substances are perhaps the organic acids, sugar, amino acids, and certain protein decomposition products such as have been described by Bondzynski and Gottlieb,[25] by Cloetta [26] and later by Pregl [27] under the name of "oxyproteic acids."

According to earlier researches, the two ratios under discussion seemed to be fairly constant in the urines of normal adults. Benedict and Miller [28] reported an average $\frac{C}{N}$ of 0.73 and $\frac{Cal}{N}$ of 8.09 as a result of fifty-eight metabolism studies. The variations among the different individuals was small, 0.67 to 0.89 and 7.3 to 8.94 respectively. Magnus-Alsleben [29] states that $\frac{C}{N}$ ratio varies in normal individuals between 0.7 and 1.0 and furthermore that the variations do not depend on the diet when this is kept within ordinary limits. Tangl [30] found a slight increase following a meal extraordinarily rich in carbohydrate. The ratios, however, were no higher than those obtained by Magnus-Alsleben. Benedict and Miller [28] were unable to find any change in the ratio which could be ascribed to variations in diet. An increase in the ratio, however, has been found during fasting (Benedict,[31] Benedict and Diefendorf [32]) in mountain sickness (Loewy [33]) and following severe muscular exercise (Magnus-Alsleben [29]), (Higgins and Benedict [34]).

As far as infants are concerned, the first examination of the $\frac{C}{N}$ was done by Rubner and Heubner [35] on one normal breast fed infant. They found a high $\frac{C}{N}$ ratio, 1.26. Van Oordt [36] working with two breast fed infants one of which was receiving an extra carbohydrate feeding, and Langstein and Meyer [37] working with several breast fed infants found also a high $\frac{C}{N}$ ratio in the urine. They did not determine the $\frac{Cal}{N}$ ratio. They attribute the high ratios to the presence in the urine of "extractive substances" from the breast milk. These findings are at variance with those described by other authors working with

25. Bondzynski and Gottlieb: Centralbl. f. Med. Wissenschaft **35**:577, 1897.
26. Cloetta: Arch. f. exp. Pathol. u. Pharmakol. **40**:29, 1898.
27. Pregl: Arch. f. Physiol. **75**:87, 1899.
28. Benedict and Miller: U. S. Dept. of Agriculture, Office of Exper. Stat., Bull. No. 175, p. 144, 1907.
29. Alsleben M.: Ztschr. f. klin. Med. **68**:358, 1909.
30. Tangl: Quoted by Magnus Alsleben.[29]
31. Benedict: Carnegie Inst. Washington, D. C., 1907, Publ. No. 77.
32. Benedict and Diefendorf: Am. J. Physiol. **18**:362, 1907.
33. Loewy: Quoted by Higgins and Benedict.[34]
34. Higgins and Benedict: Am. J. Physiol. **28**:291, 1911.
35. Rubner and Heubner: Ztschr. f. Biol. **1**:36, 1898.
36. Van Oordt: Ztschr. f. Biol. **43**:46, 1902.
37. Langstein and Steinitz: Jahrb. f. Kinderh. **61**:94, 1905.

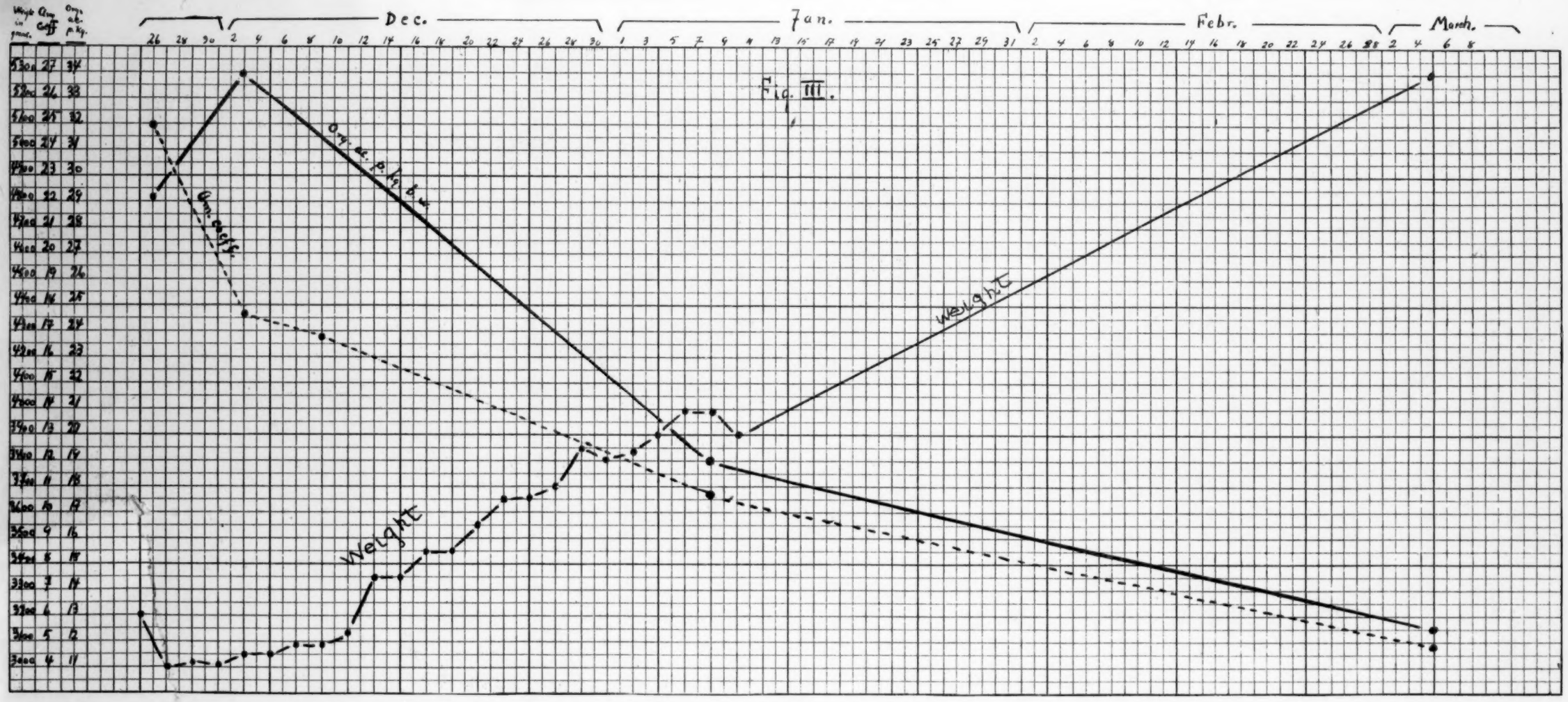

Fig. 3.—This chart shows relationship between nutritional condition, organic acid excretion in the urine and ammonia coefficient.

adults who found little or no effect of the diet on the ratios. If these figures were correct one would have to assume a different behavior of the infant's organism.

In my own experiments the caloric value of the urine was determined in the Riche adiabatic bomb calorimeter. The urine was prepared for combustion according to the method of Higgins and Benedict.[34] The urine was collected every hour without added preservative and immediately placed on ice. The urine was dried in a current of air at room temperature after the addition of an accurately weighed portion of salicylic acid and then burned in the bomb. It has been shown by Higgins and Benedict that the loss of nitrogen by this method of drying is less than 2 per cent. After the urine was burned in the bomb, the carbon dioxide formed during combustion was determined according to the method of Fries [38] by passing the gas through freshly prepared soda lime. The absorbed carbon dioxid was determined gravimetrically. The remaining carbon dioxid in the bomb was thoroughly washed out by the passage of 9 liters of carbon dioxid free air. In calculating the results in the combustion due allowance was made for the heat of combustion of the salicylic acid and for the heat developed in the calorimeter by the action of the electric stirrer.

Total nitrogen in the urines was determined on the fresh specimens by the Kjaldahl method. Each specimen of urine was tested for sugar (Benedict method) and for albumin (heat and acetic acid). The results appear in Tables 2 and 3.

In Table 2 are shown the results of experiments in which only the caloric nitrogen ratio was determined and not the carbon nitrogen. As will be seen from both tables (2 and 3) the caloric nitrogen ratio for a normal baby whether breast fed or not varies from 5.7 to 9.8 and the carbon nitrogen ratio from 0.64 to 0.77. The infants suffering from acute diarrhea showed somewhat higher ratios, and those suffering from athrepsia unusually high ones with one exception (No. 14, Table 3).

Infants who were examined over a long period of time were found to show changes in the ratios corresponding to their nutritional condition. For example, infant No. 10, Table 2, was admitted in very poor condition, weight 3,080 gm., age 3 months. The $\frac{C}{N}$ ratio was at that time very high, up to 21. The baby was fed on breast milk and started very soon to improve. After five weeks the infant had gained 700 gm. and the $\frac{Cal}{N}$ ratio was quite normal. This is depicted graphically in Figure 2. The high ratios obtained in the athreptic infants would indicate that the urine contained compounds of a higher combustion value than under normal conditions. The next step was an attempt to determine the nature of these organic compounds.

38. Fries: J. Am. Chem. Soc. **31**:272, 1909.

TABLE 2.—CALORIC-NITROGEN RATIO OF INFANTS' URINE

No.	Diagnosis	Date	Age, Mos.	Wt.	Feeding	Sugar	Albumin	C.c. Urine in 24 Hrs.	Gm. Total N. in 24 Hrs.	Large Calories in 24 Hrs.	Cal / N.
1	Normal baby.....	3/10/21	1	3,550	Br. F.	—	—	50	0.132	0.92	7.0
2	Normal baby.....	2/28/21	1	4,520	Br. F.	—	—	280	0.537	4.03	7.5
3	Normal baby.....	2/13/21	18	9,300	W. M. mixt.	—	—	470	3.12	29.95	9.6
4	Normal baby.....	2/11/21	13	10,000	W. M. mixt.	—	—	640	2.22	17.25	7.7
		2/13/21	13	10,000	W. M. mixt.	—	—	500	5.74	32.96	5.7
5	Normal baby.....	1/ 7/21	4	6,300	.....	—	—	320	0.947	8.99	9.5
6	Pyloric stenosis..	1/24/21	5	2,900	W. L. M.	—	—	90	1.000	6.12	6.2
7	Acute diarrhea...	1/ 8/21	9	4,300	W. L. M.	—	+	425	1.258	13.30	10.6
		1/ 9/21	9	4,380	W. L. M.	—	+	125	1.00	11.30	11.3
		1/13/21	9	4,100	W. L. M.	—	+	110	0.792	9.18	11.6
		1/26/21	9	4,100	W. L. M.	—	+	638	2.679	35.60	13.3
8	Acute diarrhea...	1/13/21	2	4,900	W. L. M.	—	—	300	0.492	5.34	10.9
9	Malnutrition.....	2/18/21	2	3,250	W. L. M.	—	—	195	0.702	7.56	10.8
		2/19/21	2	3,250	W. L. M.	—	—	200	0.512	3.84	7.5
10	Athrepsia.....	2/18/21	3	3,180	Br. F.	—	—	230	0.763	14.6	19.2
		2/19/21	3	3,200	Br. F.	—	—	200	0.616	8.17	13.2
		2/20/21	3	3,250	Br. F.	—	—	430	0.43	9.04	21.0
		2/28/21	3	3,400	Br. F.	—	—	500	0.520	5.99	11.5
		3/ 1/21	3	3,450	Br. F.	—	—	620	0.768	6.19	8.5
		3/ 2/21	3	3,500	Br. F.	—	—	580	0.881	7.52	8.5
		3/17/21	4	3,680	Br. F.	—	—	346	1.204	8.64	7.2
		3/18/21	4	3,680	Br. F.	—	—	425	0.884	4.60	5.2
		3/19/21	4	3,680	Br. F.	—	—	300	0.600	3.60	6.0
		3/21/21	4	3,780	Br. F.	—	—	460	1.177	7.82	6.6
11	Athrepsia.....	2/ 7/21	1½	2,530	W. L. M.	—	—	300	0.396	5.64	14.4
12	Athrepsia.....	1/15/21	3½	3,500	Br. F.	—	—	410	0.541	8.12	15.0
13	Athrepsia.....	3/29/21	2	2,680	W. L. M.	—	—	244	0.517	6.20	11.9
14	Athrepsia.....	4/20/21	2	2,850	W. L. M.	—	—	332	0.575	6.75	11.7
		4/21/21	2	2,900	W. L. M.	—	—	279	0.658	7.23	10.9
		4/22/21	2	2,950	W. L. M.	—	—	230	0.340	5.04	14.8

TABLE 3.—CALORIC-CARBON-NITROGEN RATIO OF INFANTS' URINE

Number	Diagnosis	Date	Age, Mos.	Weight	Feeding	Sugar	Albumin	C.c. Urine in 24 Hours	Gm. Total N. in 24 Hours	Large Cal. in 24 Hours	Total Cal. in 24 Hours	Cal. / N.	C / N.
1	Normal baby.....	2/25/21	2	3,690	Br. F.	—	—	260	0.70	6.91	0.54	9.8	0.77
		2/28/21	2	4,000	Br. F.	—	—	280	0.49	4.45	0.35	9.0	0.72
2	Normal baby.....	2/12/21	13	10,100	Inf. D.	—	—	580	3.06	24.82	1.96	8.1	0.64
3	Normal baby.....	2/12/21	18	9,300	Inf. D.	—	—	230	1.01	8.48	0.65	8.4	0.65
4	Normal baby.....	2/25/21	1	4,520	Br. F.	—	—	190	0.47	4.56	0.34	9.7	0.74
5	Normal baby.....	5/ 2/21	..	.....	W. M. mix.	—	—	600	2.90	19.77	1.74	6.8	0.64
		5/ 2/21	..	.....	W. M. mix.	—	—	564	3.61	22.89	2.24	6.3	0.62
		5/ 2/21	..	.....	W. M. mix.	—	—	420	2.68	25.65	2.28	9.6	0.85
6	Parenteral infec. .	7/ 7/21	16	12,000	W. M. mix.	—	—	440	7.48	30.32	6.16	4.9	0.53
7	Exudative diath.	3/10/21	7	4,500	W. M. mix	—	—	280	1.23	9.46	0.74	7.6	0.6
8	Tuberculous meningitis.....	2/10/21	18	9,600	W. M. mix.	—	—	170	1.7	17.0	1.68	10.0	0.99
		2/11/21	18	9,600	W. M. mix.	—	—	200	0.64	7.74	0.68	12.1	1.07
9	Acute diarrhea....	1/ 8/21	9	4,700	W. M. mix.	—	—	80	1.28	10.56	1.36	8.25	1.06
10	Malnutrition.....	2/20/21	3	3,300	W. L. M.	—	—	180	0.55	6.84	0.57	12.4	1.03
		3/ 8/21	3	3,300	W. L. M.	—	—	260	0.93	10.71	0.81	11.5	0.87
11	Athrepsia.....	1/24/21	3	3,200	Br. F.	—	—	130	0.26	6.34	0.52	24.4	2.00
		1/28/21	3	3,250	Br. F.	—	—	680	0.82	10.2	0.99	12.4	1.22
		2/ 1/21	3	3,300	Br. F.	—	—	420	0.47	4.99	0.79	10.6	1.7
		2/10/21	3	3,450	Br. F.	—	—	350	0.52	6.47	0.75	12.4	1.45
12	Athrepsia.....	3/24/21	3	1,930	Br. F.	—	+	180	0.31	6.61	0.61	21.3	2.00
		3/25/21	3	1,970	Br. F.	—	+	140	0.18	3.19	0.42	17.7	2.3
		3/26/21	3	1,980	Br. F.	—	+	290	0.46	6.35	0.69	13.7	1.5
		3/27/21	3	2,000	Br. F.	—	+	300	0.60	7.20	0.87	12.0	1.48
13	Athrepsia.....	4/19/21	2	2,620	W. L. M.	—	—	220	0.38	6.14	0.54	16.1	1.42
14	Athrepsia.....	4/26/21	1	2,600	W. L. M.	—	+	40	0.39	4.65	0.36	11.9	0.93

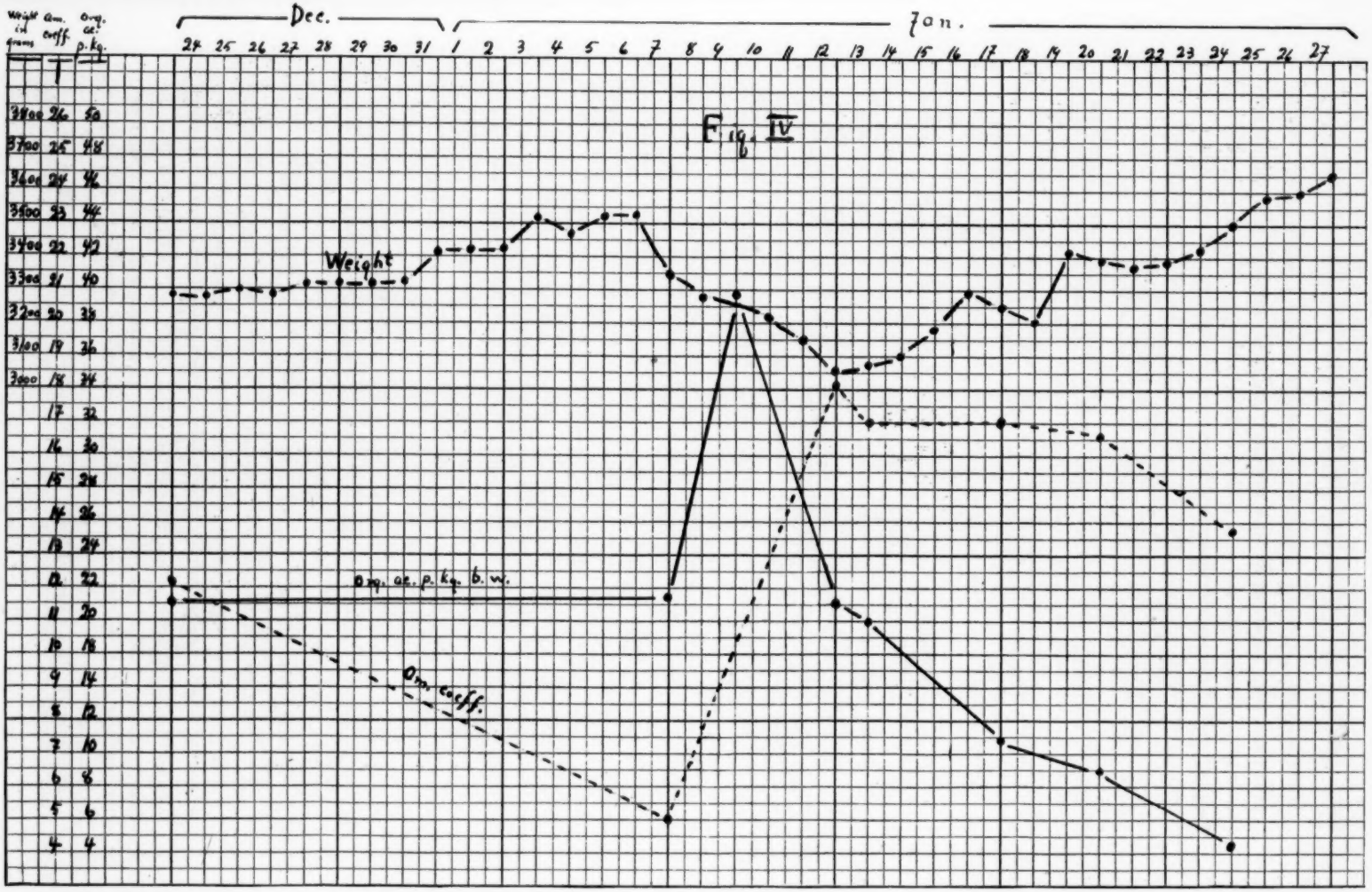

Fig. 4.—This chart shows relationship between nutritional condition, organic acid excretion in the urine and ammonia coefficient.

The normal urinary constituents which would raise this ratio are creatinin, uric acid and the amino acids if present in excessive amounts. Determinations of each of these substances in the urines of the athreptic infants were made.

TABLE 4.—CREATININ OUTPUT IN 24 HOURS

No.	Diagnosis	Date	Age, Mos.	Weight	Feeding	Mg. Total Creatinin	Mg. Creatinin per Kg. Body Weight
1	Normal baby	9/ 2/20	7	7,900	W. M. mix.	72.0	9.1
		9/ 8/20	7	7,900	W. M. mix.	72.0	9.1
2	Normal baby	12/ 9/20	20	10,800	Inf. feed.	115.5	10.5
3	Tuberculosis	9/ 3/20	10	6,200	Inf. feed.	50.0	8.06
		9/ 4/20	10	6,200	Inf. feed.	47.7	7.7
		9/ 5/20	10	6,200	Inf. feed.	25.5	4.03
4	Pneumonia	12/15/20	18	13,888	Inf. feed.	58.0	4.10
5	Exudative diathesis	3/10/21	7	4,500	W. M. mix.	28.0	6.20
6	Creatinism	9/14/20	6	3,100	W. L. M.	56.0	18.6
		9/15/20	6	3,100	W. L. M.	39.9	12.8
		9/16/20	6	3,100	W. L. M.	29.3	9.4
7	Malnutrition	12/24/20	13	6,000	W. L. M.	25.16	4.1
8	Acute diarrhea	12/14/20	3½	5,200	Prot. M.	38.10	7.3
9	Acute diarrhea	9/27/20	10	5,850	W. L. M.	79.8	13.6
		9/28/20	10	5,850	W. L. M.	53.2	9.6
		9/29/20	10	5,850	W. L. M.	34.8	5.9
10	Athrepsia	9/10/20	2	2,050	Br. M.	14.2	6.9
11	Athrepsia	12/14/20	5	3,200	Br. M.	24.0	7.5
12	Athrepsia	9/ 8/20	2½	2,700	W. L. M.	11.84	4.3
		9/ 9/20	2½	2,680	W. L. M.	7.40	2.7
		9/15/20	2½	2,600	W. L. M.	10.0	3.8
		9/17/20	2½	2,500	W. L. M.	16.12	6.4
13	Athrepsia	9/20/20	8	3,870	W. L. M.	34.00	8.8
		9/23/20	8	3,800	W. L. M.	41.00	10.7
14	Athrepsia	9/23/20	10	5,300	W. L. M.	50.55	9.5
		9/24/20	10	6,280	W. L. M.	49.20	7.8
		9/25/20	10	6,220	W. L. M.	45.00	7.2
		10/27/20	10	5,200	W. L. M.	55.50	10.6
		10/28/20	10	5,150	W. L. M.	47.60	9.2
		3/18/21	10	3,680	W. L. M.	21.0	5.7
		3/19/21	10	3,680	W. L. M.	18.6	5.05
		3/20/21	10	3,700	W. L. M.	18.6	5.02
		3/21/21	10	3,780	W. L. M.	25.2	6.8
15	Athrepsia	3/10/21	1½	2,420	W. L. M.	16.0	6.6
		3/11/21	1½	2,488	W. L. M.	14.8	6.0
		3/12/21	1½	2,500	W. L. M.	29.3	11.7
		3/13/21	1½	2,540	W. L. M.	20.1	7.9
		3/14/21	1½	2,560	W. L. M.	13.6	5.3
16	Athrepsia	3/ 8/21	3	3,250	W. L. M.	41.6	12.8
17	Athrepsia	3/12/21	3	3,630	Br. M.	18.18	5.0
18	Athrepsia	3/21/21	5½	4,390	Br. M.	13.0	2.9
		4/ 4/21	5½	4,390	Br. M.	13.44	3.06
19	Athrepsia	3/24/21	8	1,930	Br. M.	10.8	5.5
		3/25/21	3	1,920	Br. M.	7.3	3.7
		3/26/21	3	1,980	Br. M.	7.2	3.6
		3/27/21	3	2,000	Br. M.	12.3	6.1
		4/ 4/21	3	2,290	Br. M.	24.0	2.8
		4/ 5/21	3	2,110	Br. M.	8.3	3.9
		4/ 6/21	3	2,140	Br. M.	9.6	4.4

CREATININ, URIC ACID, AMINO-ACIDS OF THE URINE

For the determinations of creatinin, uric acid and the amino acids, twenty-four hour specimens of urine were used. The urine bottles were collected every hour during the day and every two hours during the night. The urine was preserved with toluol and examined immediately at the end of twenty-four hours. Creatinin was determined by the method of Folin,[39] organic acid by the microchemical calorimetric

39. Folin: J. Biol. Chem. **17**:475, 1914.

method of Folin and MacCallum [40] as modified by Benedict and Hitchcock.[41] Amino acid nitrogen was determined by the van Slyke method.[42]

As far as creatinin is concerned, Hoogenhuyze and Verploegh,[43] Amberg and Morrill [44] and Simon [45] found that the creatinin nitrogen of the urine in infants ranged from 0.4 to 3.6 per cent. of the total nitrogen. Funaro [46] has made the most complete investigation of this subject. He examined four normal breast fed infants and eleven infants suffering from various conditions and ranging in age from 3 months to 3 years and found the total creatinin output per kilo of body weight in twenty-four hours to vary from 4.62 to 10.81 mg. He came to the conclusion that this output was influenced very little, if any, by the feeding and nutritional condition of the infant.

The results of my own studies appear in Table 4.

It will be seen from Table 4 that the creatinin output per kilo of body weight per day reached a high figure in the case of one infant suffering from cretinism (No. 6). In all the others the output ranged from 3 to 13 mg. The athreptic infants, as a group, showed no increase in creatinin in the urine as compared with normal infants, the amount of creatinin was indeed, if anything, somewhat lower in the case of infants in very poor nutritional condition.

Few observations have been made on the uric acid excretion in infancy. Orgler [47] found less excretion of uric acid by breast fed infants than by those artificially fed. This he attributes to the fact that breast fed infants can utilize food better than those artificially fed. A number of observations have been made on the uric acid output in newly born infants, but as the uric acid metabolism is different during this period than afterwards the results are of no special value for comparative purposes. In Table 5 are shown the results of seventy-four determinations which I have made on thirty infants.

It will be seen that the variations in uric acid excretion are large (1.5 to 40 mg. per kilo of body weight in twenty-four hours). In a single case of acute diarrhea it was as high as 78 mg. per kilo of body weight. There seemed to be no relationship between the uric acid output and the nutritional condition of the infant; it was high in the case of perfectly normal infants. It has been generally assumed, without having any reliable figures on which to base the assumption, that the

40. Folin and MacCallum: J. Biol. Chem. **13**:363, 1912.
41. Benedict and Hitchcock: J. Biol. Chem. **20**:619, 1915.
42. Van Slyke: J. Biol. Chem. **12**:275, 1912; **16**:121, 1913.
43. Hoogenhuyze and Verploegh: Ztschr. f. Physiol. Chem. **46**:415, 1905.
44. Amberg and Morrill: J. Biol. Chem. **3**:311, 1907.
45. Simon: Ztschr. f. Kinderh. **2**:1, 1911.
46. Funaro: Biochem. Ztschr. **10**:467, 1908.
47. Orgler: Jahrb. f. Kinderh. **67**:383, 1908.

TABLE 5.—Uric Acid Output in Twenty-Four Hours

No.	Diagnosis	Date	Age. Mos.	Weight	Feeding	Mg. Total Uric Acid	Mg. Uric Acid per Kg. Body Weight
1	Normal baby	9/ 2/20	7	7,900	W. M. mixt.	127.4	16.0
		9/ 8/20	7	7,900	W. M. mixt.	240.0	30.0
2	Normal baby	1/ 2/21	4	6,300	W. M. mixt.	80.7	11.2
3	Normal baby	12/ 7/20	9	7,100	W. L. M.	138.0	19.4
4	Normal baby	10/ 3/20	4½	4,850	W. L. M.	131.0	27.0
		10/ 4/20	4½	4,818	W. L. M.	159.0	33.0
5	Pneumonia	12/15/20	18	13,888	Inf. diet	125.0	9.0
6	Tuberculosis	9/ 3/20	10	6,200	Inf. diet	76.0	12.2
		9/ 4/20	10	6,200	Inf. diet	86.0	13.8
		9/ 5/20	10	6,200	Inf. diet	165.0	26.6
7	Creatinism	9/14/20	6	3,100	W. L. M.	95.0	30.6
		9/15/20	6	3,100	W. L. M.	71.3	23.0
		9/16/20	6	3,100	W. L. M.	37.0	11.9
8	Ileocolitis	9/20/20	9	6,200	W. L. M.	82.6	13.3
		10/ 1/20	9	6,000	W. L. M.	9.0	1.5
		10/ 2/20	9	5,850	W. L. M.	10.4	1.7
9	Ileocolitis	11/30/20	9	5,600	W. L. M.	77.0	14.1
10	Acute diarrhea	9/28/20	10	5,850	W. L. M.	113.7	19.2
		9/29/20	10	5,850	W. L. M.	60.0	10.2
11	Acute diarrhea	12/14/20	3½	5,200	Prot. M.	410.0	78.8
12	Acute diarrhea	12/15/20	7	5,050	W. L. M.	150.0	29.7
13	Acute diarrhea	1/ 8/21	9	4,300	W. L. M.	159.37	40 0
14	Acute diarrhea	3/10/21	7	4.500	W. M. mixt.	56.0	12.4
15	Athrepsia	10/24/20	7	4,150	W. L. M.	36.25	8.7
16	Athrepsia	10/11/20	1	2.500	Br. M.	8.50	3.4
17	Athrepsia	9/10/20	2	2,050	Br. M.	74.0	36 0
		9/11/20	2	2,050	Br. M.	27.0	13.1
18	Athrepsia	9/ 3/20	2½	2,800	Br. M.	51.0	18.2
		9/ 4/20	2½	2.900	Br. M.	51.0	17.5
		9/ 5/20	2½	3,000	Br. M.	51.0	17 0
19	Athrepsia	9/ 8/20	2½	2,700	W. L. M.	72.0	30.3
		9/ 9/20	2½	2,680	W. L. M.	30.0	11.1
		9/15/20	2½	2,600	W. L. M.	32.0	12.3
		9/12/20	2½	2,500	W. L. M.	36.4	14.5
20	Athrepsia	9/20/20	8	3,870	W. L. M.	68.8	18.0
		9/21/20	8	3.880	W. L. M.	94.3	24.2
		9/23/20	8	3,820	W. L. M.	89.1	23.0
21	Athrepsia	10/ 3/20	10	5,300	Prot. M.	158.2	29.8
		10/ 4/20	10	5,400	Prot. M.	180 0	33.3
		10/ 5/20	10	5,450	Prot. M.	125.0	22.9
		10/ 6/20	10	5,450	Prot. M.	63 0	11.5
		10/ 7/20	10	5,480	Prot. M.	127.6	23.2
		10/ 8/20	10	5,480	Prot. M.	133.7	24.3
22	Athrepsia	11/27/20	2½	2.980	Br. M.	33.7	11.3
		12/ 3/20	2½	3,050	Br. M.	42.5	13.9
		12/ 9/20	3	3,450	Br. M.	46.0	13.3
23	Athrepsia	12/14/20	5	3.200	Prot. M.	75.0	23.4
24	Athrepsia	12/14/20	4½	2,900	W. L. M.	37.0	12,7
25	Athrepsia	12/24/20	1½	3.280	Prot. M.	82.6	25 1
		1/ 9/21	2	3.280	W. L. M.	57.7	12.5
		1/10/21	2	3,250	W. L. M.	35.1	10 8
		1/14/21	2	3,050	Br. M.	112 5	36 9
		1/18/21	2	3,080	Br. M.	65 6	21 6
		1/21/21	2	3.400	Br. M.	55.5	16.4
26	Athrepsia	3/17/21	3	3.680	Br. M.	197.0	53.5
		3/18/21	3	3.680	Br. M.	56.0	15.2
		3/19/21	3	3,680	Br. M.	51.0	13.5
		3/20/21	3	3.700	Br. M.	66.2	17.9
		3/21/21	3	3,780	Br. M.	86.0	27.7
27	Athrepsia	3/10/21	1½	2,420	W. L. M.	59.5	25.0
		3/11/21	1½	2,480	W. L. M.	39.0	15.7
		3/12/21	1½	2,500	W. L. M.	49.6	19.8
		3/13/21	1½	2,540	W. L. M.	54.0	21.2
		3/14/21	1½	2,560	W. L. M.	67.9	26.5
28	Athrepsia	3/12/21	3	3.620	Br. M.	42.0	11.6
29	Athrepsia	3/24/21	3	1,980	.....	56.7	29.3
		3/25/21	3	1,920	.....	37.7	19.1
		3/26/21	3	1.980	.....	21.75	10.9
		3/27/21	3	2,000	.....	23.0	11.5
		4/ 4/21	3	2,220	.....	19.20	8 6
		4/ 5/21	3	2,110	.....	16.90	8.0
		4/ 6/21	3	2,140	.....	11 90	5.5
30	Athrepsia	3/21/21	5½	4,390	.....	15.75	3.5
		4/ 1/21	5½	4,390	.....	15.75	3.5

TABLE 6.—Amino Acid Output in 24 Hours

No.	Diagnosis	Date	Age, Mos.	Weight	Mg. Total N. per Day in 100 C.c.	Mg. Free Amino Acid N. in 100 C.c.	Per Cent. Amino Acid N. of Total N.
1	Normal baby	2/11/21	18	9,300	556	7.3	1.3
		2/12/21	18	9,200	440	4.0	0.9
		2/13/21	18	9,280	664	2.5	0.3
2	Normal baby	2/11/21	13	10,100	348	2.4	0.6
		2/12/21	13	10,100	592	5.5	0.9
		2/13/21	13	10,100	1140	6.6	0.5
3	Normal baby	11/26/20	2	5,300	420	5.5	1.0
4	Newly born	1/ 3/21	2 wks.	3,100	468	45.6	9.7
5	Normal baby	1/ 7/21	5	6,400	296	4.0	1.3
6	Normal baby	2/25/21	5½	6,500	248	7.4	3.0
7	Normal baby	2/28/21	5 wks.	3,700	232	1.7	0.7
8	Normal baby	2/28/21	6 wks.	4,000	192	8.0	4.1
		3/ 1/21	6 wks.	4,000	176	4.0	2.2
9	Normal w. n. b.	3/10/21	4 wks.	3,560	264	6.0	2.2
10	Feeding reg.	10/25/20	3 wks.	2,750	176	6.0	2.2
11	Malnutrition	11/26/20	11	4,800	236	11.0	4.6
12	Malnutrition	12/24/20	14	6,600	520	5.5	1.0
13	Ileocolitis	11/30/20	18	5,400	520	18.75	2.6
14	Ileocolitis	11/30/20	9	5,600	360	36.0	10.2
15	Ileocolitis	12/ 2/20	9	6,200	268	25.0	9.3
16	Ileocolitis	12/15/20	8	6,000	420	12.6	3.0
17	Acute diarrhea	12/14/20	3½	5,200	320	15.4	4.8
18	Acute diarrhea	1/ 8/21	9	4,300	296	6.0	2.0
19	Pyloric stenosis	12/ 9/20	4	2,650	400	3.3	0.8
		2/ 2/21	5	3,000	800	14.0	1.7
20	Pyloric stenosis	1/ 3/21	2	2,600	264	5.5	2.0
		1/ 6/21	2	2,700	252	11.0	4.3
21	Athrepsia	10/16/20	11	6,100	664	15.4	2.3
		10/27/20	11	5,200	532	12.6	2.3
		10/28/20	11	5,150	332	11.0	3.3
22	Athrepsia	10/16/20	8	4,400	288	5.5	1.9
		10/17/20	8	4,300	520	1.1	0.1
		10/18/20	8	4,200	560	9.3	1.6
23	Athrepsia	11/27/20	2½	2,980	160	9.2	5.8
		12/ 9/20	3	3,450	204	5.5	2.6
		1/ 8/21	3½	4,000	280	9.3	3.3
		3/ 6/21	6	5,600	312	16.5	5.3
		3/ 8/21	6	5,600	348	11.8	3.1
24	Athrepsia	11/28/20	4	2,450	200	25.0	12.0
		12/14/20	4½	2,900	400	22.5	5.6
25	Athrepsia	12/14/20	5	3,200	560	15.4	0.5
26	Athrepsia	12/24/20	1½	3,280	360	3.3	0.9
		1/18/21	2	3,250	136	8.8	5.9
		1/21/21	2	3,400	120	3.8	3.2
27	Athrepsia	1/28/21	3	3,250	120	8.8	7.3
		2/ 1/21	3	3,300	112	5.5	4.9
		2/10/21	3½	3,450	148	6.6	4.5
		2/15/21	3½	3,500	132	1.32	1.0
		2/17/21	3½	3,440	324	1.7	0.3
28	Athrepsia	2/18/21	3	3,180	332	3.5	1.0
		2/19/21	3	3,200	308	18.7	6.0
		2/20/21	3	3,250	100	3.5	3.5
		2/28/21	3	3,400	104	8.8	8.4
		3/ 1/21	3	3,450	124	8.8	7.0
		3/ 2/21	3½	3,500	152	11.8	7.7
		3/17/21	3½	3,680	348	11.8	3.3
		3/18/21	3½	3,680	208	6.6	3.1
		3/19/21	3½	3,680	200	8.2	4.1
		3/20/21	3½	3,700	160	10.2	6.2
		3/21/21	3½	3,780	256	8.2	2.6
29	Athrepsia	3/10/21	1½	2,420	304	8.2	2.6
		3/11/21	1½	2,480	296	7.4	2.4
		3/12/21	1½	2,500	380	10.2	2.6
		3/13/21	1½	2,540	304	10.2	3.2
		3/14/21	1½	2,560	216	7.4	3.4
		3/28/21	2	2,750	332	4.9	1.1
		3/29/21	2	2,680	212	2.7	1.2
30	Athrepsia	3/12/21	3	3,620	228	6.6	2.8
31	Athrepsia	3/24/21	3	1,930	172	9.0	5.2
		3/25/21	3	1,970	132	9.0	6.8
		3/26/21	3	1,980	160	15.0	9.3
		3/27/21	3	2,005	200	2.9	1.4

amino-acid excretion was increased in the severe nutritional disturbances. Bahrdt and Edelstein [48] found in infants urine such varying results that from their work it is impossible to come to any conclusion as to the excretion either in normal or pathologic cases. They found in one athreptic infant an amino acid output of 10 per cent. of the total nitrogen. According to Hadlich and Grasser the amino-acid output is independent of the condition of the infant and bears no relationship to the feeding. In one condition both Simon [45] and Hadlich and Grosser [49] are in agreement as to an increased excretion of amino acids. This condition is "alimentary intoxication."

TABLE 7.

No.	Diagnosis	Age, Mos.	Weight	Total Organic Acids	Organic Acid per Kg. of Body Weight
1	Syphilis, congenital	3½	2,800	13.2	4.7
2	Parenteral infection	9	7,100	124.2	17.4
3	Parenteral infection	13	6,600	126.0	19.0
4	Acute diarrhea	3	5,200	88.0	17.0
5	Acute diarrhea	9	4,570	78.0	17.0
6	Acute diarrhea	9	4,300	170.0	41.5
7	Ileocolitis	9	5,600	74.8	11.7
8	Ileocolitis	4	5,050	30.0	5.9
9	Pyloric stenosis	4	2,650	20.4	7.6
		4	3,000	22.5	7.5
10	Pyloric stenosis	2	2,600	20.0	7.6
		2	2,700	30.0	4.1
11	Malnutrition	3	4,880	90.0	18.4
12	Normal baby	20	10,200	735.0	6.8
13	Normal baby	½	3,040	26.25	8.6
14	Normal baby	5	6,300	80.70	12.8
15	Normal baby	2	3,250	35.00	10.7
16	Normal baby	2	3,690	46.8	12.4
17	Normal baby	2	3,800	44.8	11.7
18	Normal baby	1	4,430	32.3	7.2
19	Normal baby	1½	4,500	50.4	11.2
20	Normal baby	8	6,880	72.0	10.4
		8	6,900	56.4	8.1
21	Parenteral infection	16	12,000	52.8	4.4
		16	12,000	71.5	5.9
		16	12,000	122.5	11.0
		16	11,050	71.2	6.4

My own figures as a result of seventy-two examinations on thirty-one infants show that the amino-acid nitrogen output as expressed in the terms of percentage of total nitrogen excretion vary from 0.1 to 12 per cent. The highest figure in normal infants was 9.7 in one newly-born infant. Otherwise the amount was not more than 4.1 per cent. In a very few instances athreptic infants show an increased excretion of amino-acid nitrogen but this was not at all constant.

It is thus seen that neither creatinin, uric acid nor amino-acids in the urine can account for the high carbon nitrogen and caloric nitrogen ratio in the athreptic infants. I have, therefore, looked for other substances.

48. Bahrdt and Edelstein: Quoted by Czerny and Keller, Lehrb. der Kindesernährung, **2**:494.

49. Hadlich and Grosser: Jahrb. f. Kinderh. **73**:421, 1911.

ORGANIC ACIDS IN THE URINE

As has been previously mentioned, several observers have reported a high ammonia excretion in the urines of athreptic infants. This might be interpreted as evidence of increased excretion of acid but Keller was unable to find any increase in the organic acids of the urine; this was perhaps due to the fact that at that time no entirely satisfactory method was available. Recently van Slyke and Palmer [50] have described a method which permits of an accurate determination of the organic acids of the urine. They find the normal organic acid excretion of the adult is between 8 and 11 c.c. of tenth normal acid per kilo of body weight. On applying this method to infants I have found the organic acid excretion to be approximately the same as that found in adults (Table 7).

Infants suffering from acute diarrhea show a considerable increase in the excretion of organic acids. On applying the same method to the urines of a number of athreptic infants a very considerable increase in organic acid excretion was found in every instance (Table 8).

The ammonia in the urines of these infants was also determined (Folin's method.[51])[52] A high excretion of ammonia was found as compared with normal infants and this ammonia excretion was, in a general way, proportionate to the amount of organic acids in the urine. From this one would be led to suppose that the high ammonia coefficient was directly the result of the increased organic acids.

With improvement in the infant's general nutritional condition, both organic acids and ammonia of the urine approached normal levels. This is shown graphically in Figures 3 and 4.

The next question which arises is as to the nature and source of these organic acids. One might suspect that they were the acids of the acetone body series excreted on account of partial starvation. Another possibility would be that they were acids produced from the bacterial decomposition of carbohydrates and fats in the gastro-intestinal tract and absorbed and excreted unchanged. These acids might also represent incompletely metabolized products of any of the three main foodstuffs.

In order to determine the effect of the fat intake on the excretion of organic acids in the urine, an athreptic infant who during a four day period excreted 28, 28, 23, 23, c.c. of tenth normal organic acids in the urine per kilo of body weight while on a formula containing 1.6 per cent. of fat was fed on a mixture otherwise the same but containing

50. Van Slyke and Palmer: J. Biol. Chem. **41**:567, 1920.

51. Folin: J. Biol. Chem. **29**:329, 1917.

52. The strictest precautions were taken to prevent decomposition of the urine previous to the ammonia determination. It was collected under toluene at short intervals and immediately transferred to the ice box.

TABLE 8.—Total Organic Acid Output and Ammonia Coefficient of Infants Suffering from Athrepsia

No.	Date	Weight	Age, Mos.	C.c. Urine in 24 Hrs.	Mg. Total N. in 100 C.c. Urine	Mg. NH_3 N. in 100 C.c. Urine	Per Cent. NH_3 N. of Total N.	C.c. Total Organic Acid in 24 Hrs.	C.c. Total Organic Acid per Kg. Body Weight
1	11/27/20	2,980	2½	200	160	40.0	25.0	88.0	29.3
	12/ 3/20	3,050	2½	170	188	33.2	17.6	101.32	34.0
	12/ 9/20	3,450	3	200	204	33.2	16.2		
	1/ 8/21	4,000	3	450	280	30.0	10.7	76.5	19.1
	3/ 6/21	5,600	6	500	312	15.0	4.8	70.0	12.5
2	12/14/20	2,900	4½	100	400	24.0	6.0	13.3	4.5
	12/16/20	2,950	4½	285	80	40.0	50.0	114.0	38.0
	12/17/20	2,950	4½	500	80	16.0	20.0	175.5	58.0
	12/18/20	3,000	4½	285	128	24.0	18.7	142.8	25.0
	12/19/20	3,050	4½	275	80	36.0	45.0	140.0	47.5
	12/20/20	3,050	4½	425	80	40.0	50.0	168.0	54.0
3	1/24/21	3,200	3	125	200	26.0	13.0	57.5	18.0
	1/28/21	3,250	3	180	120	20.0	16.6	68.0	21.2
	2/ 1/21	3,300	3	420	112	16.0	14.2	25.2	8.4
	2/10/21	3,450	3½	350	148	15.4	10.4	22.0	6.5
	2/15/21	3,500	3½	410	132	12.4	13.1	49.2	14.6
	2/17/21	3,440	3½	380	324	33.2	10.2	53.2	15.2
4	12/24/20	3,280	1½	285	300	44.0	12.2	71.2	21.2
	1/ 8/21	3,280	2	70	1320	66.0	5.0	70.0	21.5
	1/10/21	3,250	2	52	...	....	....	123.7	38.6
	1/13/21	3,050	2	100	220	40.0	18.1	63.0	21.0
	1/14/21	3,080	2	300	320	56.0	17.0	60.0	20.0
	1/18/21	3,250	2	355	136	24.0	17.0	35.5	10.9
	1/21/21	3,400	2	300	120	20.0	16.6	30.0	9.0
	1/25/21	3,500	2	312	144	20.0	13.8	15.0	4.3
5	10/ 3/20	5,300	10	113	520	56.0	10.7	141.25	26.6
	10/ 4/20	5,400	10	360	372	60.0	16.1	136.0	25.1
	10/ 5/20	5,450	10	500	284	64.0	27.5	190.0	35.5
	10/ 6/20	5,450	10	360	320	52.0	16.7	136.0	35.2
	10/ 7/20	5,480	10	550	320	48.0	15.0	115.0	20.2
	10/ 8/20	5,480	10	535	340	40.0	11.7	107.0	19.0
6	3/10/21	2,420	1½	350	304	13.2	4.3	35.0	14.5
	3/11/21	2,480	1½	275	296	25.6	8.4	98.0	39.5
	3/12/21	2,500	1½	320	380	16.0	4.2	96.0	38.4
	3/13/21	2,540	1½	290	304	20.0	6.5	75.4	30.0
	3/14/21	2,560	1½	367	216	32.0	14.8	95.4	38.1
	3/28/21	2,750	2	319	332	14.0	4.2	26.5	27.8
	3/29/21	2,680	2	244	212	27.8	13.1	53.6	20.0
7	2/18/21	3,180	3	320	332	47.0	13.8	74.2	26.0
	2/19/21	3,200	3	210	308	40.0	13.0	72.0	24.0
	2/20/21	3,250	3	430	100	27.4	27.4	51.6	16.0
	2/28/21	3,400	3	500	104	16.0	15.3	90.0	26.4
	3/ 1/21	3,450	3	620	124	16.0	12.9	74.0	21.8
	3/ 2/21	3,500	3	580	152	18.0	11.9	58.0	16.5
	3/17/21	3,680	3½	346	348	37.6	9.7	83.04	22.5
	3/18/21	3,680	3½	425	208	78.0	23.0	59.50	16.1
	3/19/21	3,680	3½	300	200	25.0	19.5	36.0	9.8
8	3/21/21	4,390	5½	100	248	21.8	8.8	20.0	4.5
	4/ 1/21	4,390	5½	217	180	18.8	10.4	56.4	12.8
9	3/24/21	1,930	3	180	172	38.8	20.2	68.4	35.4
	3/25/21	1,970	3	134	132	21.8	16.5	62.2	31.0
	3/26/21	1,980	3	290	160	25.0	15.6	63.8	32.2
	3/27/21	2,000	3	303	200	22.4	11.2	30.3	15.1
	4/ 4/21	2,220	3	244	260	26.0	10.0	117.12	52.7
	4/ 5/21	2,110	3	138	208	....	12.0	38.6	18.3
	4/ 6/21	2,140	3	176	240	20.4	8.0	59.84	27.8
10	4/14/21	2,600	3	268	376	26.4	6.2	75.04	28.8
	4/15/21	2,600	3	287	352	20.0	5.6	74.62	28.7
	4/18/21	2,660	3	308	320	23.0	7.2	61.6	23.1
	4/19/21	2,620	3	221	176	40.0	22.7	66.3	23.2
	4/20/21	2,850	3	232	248	33.0	13.3	74.24	25.5
	4/21/21	2,900	3	279	236	28.4	12.03	72.54	24.9

4.3 per cent. fat. On this high fat feeding the volatile fatty acids in the stools increased from 85 c.c of tenth normal acid to 112 c.c. The organic acid output in the urine remained, however, practically the same, that is to say, 24 c.c. tenth normal acid per kilo of body weight. The ammonia coefficient was also unchanged. Another infant 16 months of age suffering from otitis media but in good nutritional condition while fed on a milk mixture containing 1.9 per cent. fat excreted 4.5 and 5.9 c.c of tenth normal organic acid on two consecutive days. The fat in the food was then increased to 4.8 per cent., the other constituents remaining the same, and the child excreted 11.1 and 6.4 c.c. of tenth normal organic acid per kilo of body weight per day. The ammonia coefficient on the low fat days ran from 3.1 to 4 per cent.; on the high fat days 4.2 and 4. We thus see a relatively small increase in the excretion of organic acids and of ammonia following a very great increase in the fat of the diet. These results are quite comparable to those of Howland and Cook [53] who found no increase in the ammonia of the urine in infants receiving enormous amounts of fat.

Mention has already been made of the fact that there is an insufficient amount of amino-acids in the urine to account for the large amount of organic acid present. Most of the common organic acids, particularly those of the fatty acid series, are soluble in ether. In an attempt to separate these acids from the urine for further identification the urines of these infants were extracted with ether with a surprising result that only 20 per cent. of the acids present were extractable. The nature of these organic acids which are insoluble in ether has not yet been determined. Certainly they are not acids of the acetone body series nor lactic acid.

With the evidence at hand we can only assume that these acids are the results of a disturbed metabolism and represent products which would, under normal conditions, be completely broken down. Such a disturbance of metabolism would, if continued over a considerable length of time, naturally affect the nutrition. The evidence is that the cause of the disturbed metabolism is deep seated and that many of the cells of the body are involved, it would not seem unreasonable that the cells of the gastro-intestinal tract also suffer. If the poor circulation which has been found to occur in the peripheral parts of the body of these infants were also present in the gastro-intestinal tract it would contribute to increase the pathological changes in the cellular function of the intestinal tract. The importance of the circulatory factor in these conditions has been especially emphasized by Marriott.[18] With a lowered functional capacity of the cells of the gastro-intestinal tract the power of absorption would naturally be lowered. In order to obtain

53. Howland and Cooke: Trans. Am. Ped. Soc. **12**:130, 1910.

some idea of the absorptive power of the intestinal tract of these infants, some determinations of the total caloric intake and output have been made (Table 9).

ABSORPTION OF FOOD FROM THE INTESTINAL TRACT

The total caloric intake and output of ten infants were examined. One of these was convalescing from pyloric stenosis and one was suffering from a parenteral infection, one was perfectly normal, and the seven others were in a condition of more or less advanced athrepsia. In all

TABLE 9.—CALORIC INTAKE AND LOSS IN 24 HOURS

No.	Diagnosis	Date	Weight	Age, Mos.	Total Cal. Int.	Total Cal. Stools	Total Cal. Urine	Per Cent. Total Cal. Loss of Intake
1	Athrepsia	4/25/21	2,600	1½	326	81	5.6	26.5
		5/15/21	2,750	2	385	37	2.62	10.5
		5/16/21	2,800	2	296	19	2.96	7.4
2	Athrepsia	2/ 1/21	3,300	3	399	45	5.04	12.2
		2/10/21	3,450	3	453	59	6.40	14.3
		2/15/21	3,500	3	440	18	8.11	6.0
3	Athrepsia	2/ 7/21	2,530	1½	866	161	1.88	19.0
4	Athrepsia	2/18/21	3,180	3	594	34	14.16	18.2
		2/19/21	3,200	3	521	92	8.17	19.1
		2/20/21	3,250	3	534	60	9.04	13.0
		2/28/21	3,400	3	481	66	5.99	7.6
		3/ 2/21	3,500	3	455	31	7.52	8.5
		3/17/21	3,680	3½	674	41	8.64	7.4
		3/18/21	3,680	3½	674	45	4.60	7.4
		3/19/21	3,680	3½	490	45	3.60	9.9
		3/20/21	3,700	3½	461	28	8.40	7.9
		3/21/21	3,780	3½	540	35	7.82	8.0
5	Athrepsia	3/10/21	2,420	1½	376	53	5.0	15.4
		3/11/21	2,480	1½	376	49	4.4	14.5
		3/12/21	2,500	1½	326	54	6.7	18.7
		3/13/21	2,540	1½	387	43	4.7	13.3
		3/14/21	2,560	1½	274	45	6.9	19.0
		3/28/21	2,750	2	336	30	6.6	10.9
		3/29/21	2,680	2	292	41	6.07	16.0
6	Athrepsia	3/24/21	1,930	3	426	80	6.40	20.4
		3/25/21	1,970	3	321	80	3.00	22.5
		3/27/21	2,000	3	261	58	7.22	22.20
7	Athrepsia	4/20/21	2,850	2	448	79	6.75	19.3
8	Parenteral infection	5/ 7/21	12,000	16	661	81	30.3	16.8
		5/ 8/21	12,000	16	593	66	30.0	16.2
		5/ 9/21	12,000	16	846	61	44.0	11.3
9	Pyloric stenosis	3/ 2/21	2,400	5	537	32	13.0	8.4
		2/ 5/21	2,400	5	981	50	13.9	6.5
10	Normal baby	5/ 2/21	6,880	8	865	60	19.7	9.17
		5/ 3/21	6,880	8	945	32.4	22.8	5.8
		5/ 4/21	6,900	8	904	78	25.6	11.4

but one instance the experiment was carried out over a number of days. Combustion of the urine and stools were made in the Riche bomb calorimeter in the manner described above. The total caloric value and not the physiological value was considered. The results appear in Table 9. From this it will be seen that the normal infant studied and the one with pyloric stenosis who was in a fair condition showed a figure approximating that which has previously been determined on normal infants. For example, Rubner and Huebner found a total caloric loss which was 7.3 per cent. of the caloric intake. The seven

athreptic infants all showed a greatly increased loss of the combustible material in the excreta, in one instance as high as 26 per cent. of the total intake. With improvement in the general condition of the infants, there was a much lessened loss of material, in some instances the loss falling to entirely normal figures after a period of improvement. In Figure 2 is shown graphically the relationship between gain in weight, caloric loss in the stools and the caloric nitrogen ratio of one of these infants (No. 4).

From these results we would seem to be justified in assuming a marked lack of absorption in the case of infants suffering from advanced athrepsia. This finding supports very well the hypothesis of Huebner and of Marriott that absorption of an insufficient amount of food also plays a role in explaining the poor nutritional condition of these infants. The fact that the same infant after improving shows a normal absorption points to the fact that we are dealing with a purely functional disturbance.

It is not my intention to discuss now the etiology of athrepsia, but rather the changes in the metabolism which occur once the condition has developed. The infants here studied were those in whom infection has been excluded and the chief cause for their condition would seem to have been the fact that they were artificially fed. We know that even a normal infant's intestinal tract has somewhat less absorptive power for artificial feeding than breast milk, furthermore, the majority of infants fed artificially actually receive a smaller amount of food than those nourished at the breast. This would lead to under-nutrition. It is difficult to evaluate the influence of the hereditary or constitutional factor as emphasized by Czerny. We know that even in adults there is a great difference in the reaction towards food and surroundings; such differences are even more marked during the period of infancy and it would seem quite likely that certain infants are less capable of adapting themselves to artificial feeding than are others and it is the infants of this group that fall into the condition of athrepsia when deprived of the natural nourishment. One of the first effects of failing nutrition is, perhaps, in the circulatory system which is later followed by changes in the intermediary metabolism and functional disturbance in the intestinal tract. No single factor will explain the picture but together they contribute in developing the athreptic condition.

SUMMARY

1. In the case of infants suffering from the condition of athrepsia there is a diminished capacity of the organism to bring about such oxidations as the transformation of benzol to phenols.

2. In the urine of athreptic infants the caloric nitrogen and carbon nitrogen ratios are high as compared to normal infants. This is an indication of excretion of an excessive amount of organic material containing little or no nitrogen.

3. There is no increase in the urinary excretion of creatinin, uric acid or amino-acid nitrogen in the urine of athreptic infants.

4. During the severe stages of athrepsia there is an increased excretion of organic acids in the urine (as determined by titration).

5. The ammonia excretion in the urine of athreptic infants is in a general way proportionate to the amount of organic acids present.

6. With improvement in the nutritional condition the excretion of organic acids and of ammonia decreases.

7. The organic acids in the urine of athreptic infants are for the greater part insoluble in ether.

8. There is a greatly increased loss of food material in the stools during the severe stages of athrepsia. This loss as determined by the bomb calorimeter may be as great as 26 per cent. of the food intake. With improvement in the nutritional condition of the infant the utilization of food is much greater.

ON THE ETIOLOGY OF HEMORRHAGIC DISEASE OF THE NEW-BORN *

C. F. GELSTON, M.D.
SAN FRANCISCO

The problem presented by the various hemorrhagic conditions occurring in infancy and childhood, as well as those associated with morbid states in adults, has been extensively studied, but until recently, with confusing and inconsistent results. This is especially true of the condition known as "hemorrhagic disease of the new-born," called by many English writers "hemophilia of the new-born."

The following case report, with the results of the study of the factors of coagulation, is submitted as further evidence tending to clarify the problem of the etiology of the disease.

REPORT OF CASES

History.—Hospital No. 10898. Baby M, male, born Feb. 25, 1916, after a normal pregnancy and labor, entered the hospital February 28 for persistent omphalorrhagia which had had its onset early the day of entry. The family history was negative except for the presence of a + + + positive Wassermann reaction in the father's blood serum. The mother's Wassermann reaction on two occasions was negative. No history of bleeding could be obtained in other members of the family.

Physical Examination.—Essentially negative, other than for the presence of a constant oozing of blood from the base of the cord which could not be controlled by bandages, epinephrin, horse serum, or kephalin.

The kephalin used was prepared according to the method of Howell. Dried and powdered brain tissue is extracted with ether and purified by washing with alcohol and acetone. The resulting product is a brownish-yellow gummy substance which is only slowly soluble in distilled water. For purposes of local application the substance may be applied directly in the form of an ointment or in solution.

The laboratory technic involved in the examination of the blood, was carried out as recommended by Hurwitz and Lucas.

Blood Examination.—The blood at the age of 3 days, at entry, was as follows: Hemoglobin, 75 per cent.; red blood corpuscles, 3,488,000; white blood corpuscles, 14,400; differential count: Polymorphonuclears, 43 per cent.; eosinophils, 1 per cent.; basophils, 0 per cent.; lymphocytes, 42 per cent.; large mononuclears, 14 per cent.; blood platelets, 435,000. Clotting time, whole blood, 70 minutes; recalcified plasma, 105 + minutes. Cholemia. Antithrombin normal.

The baby began rapidly to show the signs of hemorrhage, and three injections of citrated whole blood were given, one of 10 c.c. into the buttocks, two hours after entry, one of 8 c.c. into the longitudinal sinus, and one of 35 c.c. into the same vein, at half hour intervals. The bleeding was then effectually checked.

A blood count at this time, twenty minutes after the last injection, gave the following results:

Hemoglobin, 45 per cent.; red blood corpuscles, 1,968,000; white blood corpuscles, 27,600. Differential count: Polymorphonuclears, 75 per cent.; eosinophils, 0 per cent.; basophils, 0 per cent.; lymphocytes, 6 per cent.; large

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* From the Department of Pediatrics of the University of California and the University of California Hospital.

mononuclears, 13 per cent.; 1 nucleated red corpuscle; anisocytosis; poikylocytosis; blood platelets, 385,000.

Eight hours after injection of the blood, the clotting time of the patient's whole blood was 18 minutes; clotting time of whole blood of control was 7 minutes; clotting time of recalcified plasma of patient was normal; clotting time of recalcified plasma of control was normal.

Blood count: Hemoglobin, 40 per cent.; red blood corpuscles, 2,240,000; white blood corpuscles, 17,000. Differential count: Polymorphonuclears, 56 per cent.; eosinophils, 0 per cent.; basophils, 0 per cent.; lymphocytes, 30 per cent.; large mononuclears, 13 per cent.; 1 nucleated red corpuscle; secondary anemia.

A blood culture at this time was negative.

On the day of discharge, three days after entry, the blood count was: Hemoglobin, 50 per cent.; red blood corpuscles, 2,704,000; white blood corpuscles, 20,000. Differential count: Polymorphonuclears, 57 per cent.; eosinophils, 0 per cent.; basophils, 0 per cent.; lymphocytes, 22 per cent.; large mononuclears, 21 per cent.; blood plafelets, 385,000; secondary anemia.

The baby was discharged in good condition. At no time was there evidence of hemorrhage from the mucosa or elsewhere.

DISCUSSION

The clinical picture of hemorrhagic disease of the new-born is distinct and easily recognized. It is the etiology which has presented the difficulties. The first mention of the disease was made by Mauriceau [1] in 1682 but with no suggestion as to its cause. Since then many cases have been reported, with the presentation of an almost equal number of etiological factors. Lovegren,[2] in a review of the subject, mentions von Siebold's theory of gangrene of the intestine and Bulard's theory (1828) of intestinal ulcerations, the latter to be shortly denied by Gendrin and Kiwisch. Von Chrzanowski [3] demonstrated a suffusion of blood into the esophagus; Fuhrman,[4] macroscopic and microscopic lesions in the mucosa of the intestinal tract; Schöppler,[5] punctiform hemorrhages throughout the digestive canal, and Unger,[6] an acute hemorrhagic enteritis. Graham,[7] in a study of all the hemorrhagico-icteric conditions of the new-born, including Buhl's disease, Winckel's disease, icterus neonatorum, hemorrhagic disease of the new-born, etc., mentions Cruveilhier's (1827) findings of gastric ulcers, and states that this is the accepted idea of most modern observers. Ulcers have, indeed, been found by Gärtner, Rehn, Baginsky, Bar and others.[8]

Graham divides the etiologic conditions, excluding true hemophilia, into five types—syphilis, infections, mechanical factors, heredity and known chemical agents. In support of the theory of infection are Knöpfelmacher, Heubner, Runge, Bendix, Hutinel, Merklin, Holt, etc.

1. Quoted by Lövegren.
2. Lövegren: Jahrb. f. Kinderh. **78**:249, 1913.
3. Von Chrzanowski: Jahrb. f. Kinderh. **78**:249, 1913.
4. Fuhrman: Jahrb. f. Kinderh. **78**:249, 1913.
5. Schöppler: Jahrb. f. Kinderh. **78**:249, 1913.
6. Unger: Jahrb. f. Kinderh. **78**:249, 1913.
7. Graham: J. Exper. M. **15**:307, 1912.
8. Quoted by Vorpahl, Arch. f. Gynek. **96**:377, 1912.

Graham considers the factor as asphyxia or chloroform poisoning, the underlying condition being a deficiency in oxidation, of a general, local or selective character in all of these states associated with hemorrhage or icterus or both. Somewhat along these lines was the theory of Ebstein-Oesterr [9] who believed the cessation of respiration at birth with resulting asphyxia caused a great increase of vascular tension and the possibility of extravasation and ulceration of the stomach.

Von Runstedt,[10] Shukowsky [11] and Kundrat [12] found hyperemia of the intestinal vessels; Binz (1865), erosion with perforation; Landau [13] (1874) and Semple,[14] thrombosis of the umbilical vein due to asphyxia; Strassman,[15] blocking of the ductus Botalli with a thrombus; von Preuschen and Pomorski,[16] hemorrhagic infarcts in the floor of the fourth ventricle; von Franque,[17] retrograde emboli; Honen,[18] intestinal ulceration; and Schmorl,[19] widespread fatty degeneration. Stamm [20] found at necropsy in his case anemia of all the organs, subdural and subpleural ecchymoses and a necrotic ulcer of the duodenum. Simmonds [21] in four cases found respectively umbilical sepsis, atresia of the duodenum, a congenital heart lesion, and multiple hemorrhagic erosions of the intestines. Fraenkel [22] and Vorpahl [23] believe the condition incident to the local changes in the capillaries. Soresi [24] presupposes a metabolic change both in the blood and blood vessels.

Balard [25] has but two etiologic factors for consideration, the mechanical and the infectious. Ribemont considers the main cause in the former as a circulatory change due to instability of the respiratory and circulatory mechanisms resulting in congestion. Being unable to demonstrate hypertension clinically, Balard considers the essential factor as dyscrasia of the blood constituents themselves, although the theoretical possibility of the other theory cannot be gainsaid.

Bonnaire and Durante [26] adhere also to the vascular theory, as did Rindfleisch,[27] obstetrical traumatism playing a very minor rôle.

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9. Ebstein-Oesterr: Jahrb. f. Pediat. **7:** 1876.
10. Quoted by Vorpahl.
11. Shukowsky: Münch. med. Wchnschr. **59**:280, 1912.
12. Quoted by Vorpahl.
13. Quoted by Vorpahl.
14. Semple: Brit. M. J. **2**:72, 1911.
15. Quoted by Vorpahl.
16. Von Preuschen and Pomorski: Centralbl. f. Gynek., 1894.
17. Quoted by Vorpahl.
18. Quoted by Lövegren.
19. Quoted by Lövegren.
20. Stamm: Münch. med. Wchnschr. **61**:1947, 1914.
21. Simmonds: Münch. med. Wchnschr. **61**:1947, 1914.
22. Fraenkel: Münch. med. Wchnschr. **61**:1947, 1914.
23. Vorpahl: Arch. f. Gynek. **96**:377, 1912.
24. Soresi: Quoted by Schloss.
25. Balard: Bull. Soc. Obst. et de Gyn. **3**:508, 1914.
26. Bonnaire & Durante: Obst. et de Gyn. **1**:272, 1912.
27. Rindfleisch: Bonnet-Laborderie.

Syphilis without doubt plays a part, and an important one, in certain cases. Simon, Henoch, Hamill, Nicholson, etc.,[28] have found it in instances but consider it not essential. Schloss[28] had two cases and Krösing[29] one case with a syphilitic history. In Whipple's case the father was syphilitic. He had a triple positive Wassermann reaction, as noted above. Lespinasse and Fisher[30] ascribe from 2 to 6 per cent. of the cases to syphilis. Wassermann reactions in new-born children are practically consistently negative even in flagrant cases, and it is therefore possible that only by means of testing the blood of the parents can accurate statistics in regard to the influence of lues in this condition be obtained. This point is very evident in the case in question where the presence of lues in the family was not suspected and the child showed no clinical manifestations of the disease whatsoever. Wilson is a strong adherent of the theory of a close etiologic relationship between syphilis and hemorrhagic disease of the new-born.

Sepsis also may cause multiple hemorrhages; in fact, practically every known organism has been found. The clinical picture, however, of hemorrhagic disease of the new-born is not one of sepsis, as a rule. The possibility of intra-uterine infection is brought forward by Commandeur.[31] Turck,[32] in some experiments on animals, demonstrated by feeding *B. coli* to pregnant animals the possibility of causing hemorrhages, premature births and even death. This is due to the reduction of the antiferments in the serum when the bacteria are destroyed in the subareolar tissues. This furnishes then an additional hypothesis as to the cause of hemorrhagic disease.

There is comparatively little in the literature in regard to heredity, although the possibility is mentioned (Graham[7]). Pitfield[33] reported a family in which four infants in succession showed icterus with hemorrhages, two of them dying. In Reichard's[34] case, which was the ninth child, a brother had died at the age of four days of gastro-intestinal hemorrhage. Syphilis was not present in either case. Oldershaw[35] reports the presence of exophthalmic goiter in the mother. In the case reported by Swain, Jackson and Murphy,[36] the paternal grandmother had died of pernicious anemia, and a cousin had died of melena at the age of 4 days. In Jenning's[37] case also, the mother died of pernicious anemia shortly after the birth of the child.

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28. Quoted by Schloss: Am. J. Dis. Child. **1**:276 (March) 1911.
29. Krösing: Münch. med. Wchnschr. **59**:280, 1912.
30. Lespinasse and Fisher: Surg. Gyn. & Obst. **12**:40, 1911.
31. Commandeur: Bull. Soc. Obst. et de Gyn. **1**:297, 1912.
32. Quoted by Hymanson: Arch. Pediat. **32**:2, 125, 1915.
33. Pitfield: Arch. Pediat. **29**:761, 1912.
34. Reichard: J. A. M. A., **59**:1539 (Oct. 26) 1912.
35. Oldershaw: rit. M. J. **1**:1003, 1915.
36. Quoted by Lespinasse and Fisher.
37. Jennings: J. A. M. A. **60**:1154 (April 12) 1913.

One rather interesting theory is that propounded by Bonnet-Laborderie [38] based on the repeated examinations of the mother's milk in a case of hemorrhagic disease. This theory is that there is a toxic or irritative substance in the mother's milk causing changes in the gastric mucosa. There is apparently an increased hyperemia of the gastric and intestinal mucous membrane with an exaggeration of the peristalsis provoking in turn more or less active antiperistalsis and vomiting.

It was not until 1911 that particular investigation was made of the blood, in an endeavor to demonstrate the cause of the bleedings as something intrinsic in the blood itself. Schloss and Commiskey,[39] who have done a great deal of work on this condition, found inconstant results in the coagulation time. Lespinasse and Fisher [30] report the findings of Carrel, Lambert and Brewer who made the first transfusion for the disease. These observers made the statement at that time that, on account of the sudden recovery with no convalescence, infection or change in the capillaries could not be an adequate explanation. The condition must be due "to a change in the chemical condition of the blood.". "The solution of the problem of its etiology is to be found in a chemical study of the processes of osmosis in capillary vessels, of the chemistry of the coagulation of the blood, and along kindred lines which are for the most part new and untouched." As a result of Schwartz and Ottenberg's [40] case, they concluded impaired blood coagulation to be at the basis of the disease as the immediate cause of the uncontrollable hemorrhages and to be most probably due to an interference in the production of thrombokinase.

In 1912, Schloss and Commiskey [41] observed a number of cases and collected their former data. In the first case, a poor clot seemed to indicate a deficiency in fibrinogen. All the factors for coagulation were present because spontaneous clotting occurred—the coagulation itself, however, was incomplete, the clot being very easily disintegrated. There was experimental proof for the presence in adequate amounts of thrombin and calcium, the former, in fact, being actually in excess. As regards their determinations of the coagulation time, however, they are unreliable for the reason that the estimations were made either at the site of a skin puncture or from blood drawn in that manner, thus allowing contamination with tissue juices (thrombokinase) and resulting inaccuracy.

Their findings, however, were as follows: In four cases, the coagulation time was normal; in two cases, slightly delayed; in two cases, decidedly delayed; and in two cases, absent or greatly delayed. "In certain cases not explainable by deficiency or absence of thrombin

38. Bonnet-Laborderie: Bull. Soc. Obst. et de Gyn. **16**:630, 1913.
39. Schloss and Commiskey: Am. J. Dis. Child. **1**:276 (March) 1912.
40. Quoted by Lespinasse and Fisher.
41. Schloss and Commiskey: Am. J. Dis. Child. **1**:216 (March) 1912.

or fibrinogen, however, in other words, with normal coagulation of the blood, the condition seems to be due to some local vascular lesion or defect present only in the bleeding areas."

In two further cases of Schloss [42] there was in one deficiency in thrombin, in the other, deficiency in fibrinogen. Lövegren [43] ascribed the condition to faulty coagulation.

Richards [44] carried the investigation still further. He eliminated fibrinogen from consideration as a causative factor because the quantity supplied in a small amount of serum administered therapeutically would not be sufficient to cause permanent clotting. "The fault must be in the thrombokinase, salts or prothrombin. Thrombokinase may be disregarded since it comes from the tissue juices and none was allowed to contaminate the serum used. Calcium is of no value therapeutically and is ruled out on that basis." He therefore decided that the fault lay in a prothrombin deficiency due to low platelet production. In his case, the platelet count during the bleeding time was 20,000 per cmm. slowly rising to 347,000 per cmm. after the bleeding ceased.

Whipple's [45] observations on different types of bleeding, including icterus, anemias, hepatic disease, etc., showed in all but one the presence of an excess of antithrombin. In that one, namely, hemorrhagic disease of the new-born, there was a very marked deficiency, almost absence in fact, of prothrombin.

Hurwitz and Lucas,[46] in a comparative study of the blood in hemophilia, have placed the problem of that and allied conditions, together with the actual process involved in coagulation of the blood in health, on a firm basis. The bleeding in hemophilia is due to a lack of prothrombin, a loss of the prothrombin-antithrombin balance. This is of interest in relation to hemorrhagic disease in that a few authentic cases of hemophilia have manifested themselves as hemorrhagic disease shortly after birth. It is logical to suppose a blood dyscrasia with a common basis in the two conditions, prothrombin being deficient in both, but with widely different course; the one spontaneously arresting itself or capable of control, or on occasion rapidly fatal; the other a chronic condition, the organism being unable to establish the normal and necessary constituents of the blood.

In the case reported, it was possible to demonstrate at the time of the hemorrhage a practical lack of prothrombin. Within eight hours after the cessation of the hemorrhage, prothrombin was present in normal quantities. The findings not only corroborate those of Whipple, but show in addition the loss of the prothrombin-antithrombin balance and its most remarkable reestablishment. It is in regard to the latter

42. Schloss: Amer. J. Obst. **67**:820, 1913.
43. Lövegren: Jahrb. f. Kinderh. **79**:708, 1914.
44. Richards: Med. Rec. **81**:69, 1912.
45. Whipple: Arch. Int. Med. **12**:637 (Nov.) 1913.
46. Hurwitz and Lucas: Arch. Int. Med. **17**:543 (May) 1916.

point, in other words, the therapy of the disease, that the mode of action of the whole blood becomes the object of speculation.

Several possibilities present themselves. There may be simply a stimulation to the production of prothrombin; the injection may supply enough prothrombin to cause cessation of the bleeding although not fully reestablishing the balance or it may actually reestablish the balance. The latter seems hardly logical, considering the small amounts of whole blood necessary. It is more probable that a combination of the first two possibilities is involved, with a stimulation to the production of prothrombin and the addition of a sufficient quantity in itself to bring the constituents just within the margin compatible with approximately normal function.

In regard to the use of whole blood, Schloss has placed this on a firm basis, and its value has been fully demonstrated by many observers since that time (Petersen,[47] Hurwitz,[48] Berghausen,[49] Kurtz [50] Larrabee,[51] etc.). Its use is now advocated in preference to serum, defibrinated blood, gelatin, adrenalin, etc., by most observers.

The most advantageous site for the injection is the longitudinal sinus advocated by Helmholz.[52] The area of the anterior fontanel can quickly be prepared, the location of the sinus is constant, and by following the directions laid down by his experience, no difficulties need be encountered, especially since the perfection of the Goldbloom needle.

Foote [53] and Rodda [54] have recently demonstrated that hemorrhagic disease of the new-born may be a prominent factor in the causation of intracranial hemorrhage. This is of the greatest importance since in the hemorrhagic diathesis under discussion, we have the opportunity of saving a large proportion of the infants by means of medical transfusions, should the diagnosis be made early enough.

I wish to acknowledge my indebtedness to Dr. William Palmer Lucas for permission to publish this case, and to Dr. S. H. Hurwitz, formerly of the Hooper Foundation for Medical Research, who conducted the blood examinations.

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47. Petersen: J. A. M. A. **66**:1291 (April 22) 1916.
48. Hurwitz: Amer. J. M. Sc. **154**:689, 1917.
49. Berghausen: J. A. M. A. **70**:514 (Feb. 23) 1918.
50. Kurtz: J. A. M. A. **72**:1363 (May 10) 1919.
51. Larrabee: Boston M. S. Jr. **183**:151, 1920.
52. Helmholz: Am. J. Dis. Child. **11**:194 (Feb.) 1915.
53. Foote: Am. J. Dis. Child. **20**:18 (July) 1920.
54. Rodda: Am. J. Dis. Child. **19**:268 (April) 1920; J. A. M. A. **75**:452 (Aug. 14) 1920.

SEVERE INFANTILE MALNUTRITION

THE ENERGY METABOLISM WITH THE REPORT OF A NEW SERIES OF CASES*

FRITZ B. TALBOT, M.D.
BOSTON

Severe infantile malnutrition has received many names, such as infantile atrophy, marasmus, atrophy, athrepsia and decomposition. It does not represent a definite disease entity nor is there any clear description of exactly what the condition is. It is found in all degrees of severity and it is often difficult to state just when it commences. It is usually associated with symptoms of indigestion, either vomiting or diarrhea, or both, and a loss in weight. Some infection, such as pyelitis or bronchitis often complicates the condition. When most pronounced, the infant is very much wasted, the skin hangs in folds and is of a gray pallor, the hands and feet tend to be cold, and toward the end the temperature becomes subnormal and has to be maintained by external heat. Metabolism experiments show that the infant is frequently unable to absorb the food given him. There is no common pathologic basis for the symptoms found in this condition. Marriott [1] has drawn attention to the fact that there is a decrease of blood volume coincident with the malnutrition.

Most methods of study of this condition do not give results which explain what is going on in the body. This can best be shown by the energy metabolism and it is the purpose of this investigation to show the similarity between the metabolism of infants with slight loss of weight and those with severe malnutrition or so-called "atrophy." The early investigations of infantile malnutrition are not comparable since the results were not obtained under basal conditions. They will not be commented on here, but are included in the historical bibliography.

A new series of cases was studied by me during the last two years at the Massachusetts General Hospital with the assistance of Miss Margaret E. Moriarty. This series is comparable with the investigations of Benedict and Talbot,[2] Murlin and Hoobler,[3] and Fleming,[4] because the metabolism in all these studies was obtained under basal conditions.

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*From the Children's Medical Department, Massachusetts General Hospital.

1. Marriott: Am. J. Dis. Child. **20**:461 (Nov.) 1920.
2. Benedict and Talbot: Carnegie Institution of Washington, D. C., publication 201.
3. Murlin and Hoobler: Am. J. Dis. Child. **9**:81 (Jan.) 1915.
4. Fleming: Quart. J. M. **14**:54, 1921.

These cases have been charted in Table 1. They are all underweight to a greater or less degree and represent malnutrition due to a variety of causes.

TABLE 1.—Cases of Different Degrees of Malnutrition. (New Series)

Subject	Sex	Age, Mos.	Weight, Kg.	Average Weight for Age (Holt)	Total Calories	Calories per Kg.	Calories per Sq. M. (Dubois Linear)	Remarks
1	M	2¾	4.255	5.377	303	71.2	1,157	Malnutrition
2	M	14	7.055	9.940	481	68.3	1,233	Malnutrition
3	F	2½	2.600	5.165	286	110.0	1,467	Malnutrition
4	M	4½	4.000	6.534	373.5	93.3	1,680	Malnutrition
5	M	8	5.700	8.070	384	67.0	1,168	Postpneumonia
6	M	10	5.835	8.750	443	76.0	1,326	Postpneumonia
7	F	7	4.600	7.727	328	71.3	1,189	Regulation feeding; pyelitis
8	F	5	2.630	6.818	193	73.4	980	Normal temperature by means of hot water bags
9	M	9	6.500	8.490	401	61.6	1,116	Malnutrition
10	M	11	6.000	9.200	405	67.5	1,191	Rickets; secondary anemia
11	G	13	3.615	9.800	312.5	86.5	1,292	Patent ductus arteriosus
12	M	4	3.700	6.250	406.5	109.5	1,652	Regulation feeding
13	F	2	2.350	4.770	246	104.8	1,359*	Regulation feeding
14	M	7	3.325	7.727	345	103.5	1,527*	Malnutrition
15	M	5	4.300	6.818	392	91.2	1,442	Regulation feeding; diarrhea
16	M	4	4.500	6.250	350	77.7	1,247	Malnutrition
17	F	6	3.600	7.270	272	76.0	1,132	Malnutrition

* Lissauer.

Table 2 shows the comparison of the heat production of infants of like body weight and height but of different ages. It shows a higher metabolism for older infants than for younger infants of the same size. This is of significance since the older infants have a greater

TABLE 2.—Comparison of Heat-Production of Infants of Like Body-Weight and Height, but of Different Ages (Benedict and Talbot Series) *

Subject	Sex	Body Weight, Kg.	Height, Cm.	Age, Mos.	Heat Produced		
					Calories per 24 Hours	Calories per Kg. per 24 Hours	Calories per Sq. M. (Meeh) per 24 Hours
A. L.	F	3.18	53	4	226	71	876
J. V.	F	3.38	53	8½	297	88	1,108
E. N.	F	5.40	66	6	353	66	962
D. M.	M	5.18	66	11	369	71	1,034
M. M.	F	5.47	62	4½	285	52	770
J. M.	M	5.63	62	8	467	83	1,239
D. Q.	M	5.28	62	4½	305	57	846
J. P.	M	5.45	63	7	387	70	1,039
M. M.	F	5.47	62	4½	285	52	770
J. P.	M	5.45	63	7	387	70	1,039
D. Q.	M	5.28	62	4½	305	57	846
J. M.	M	5.63	62	8	467	83	1,239
L. R. B.	F	5.99	64	4	331	55	844
F. K.	M	5.71	65	7	381	67	1,003
H. T.	M	9.33	75?	5½	420	45	797
E. G.	M	9.37	74	10	479	51	907

* From Benedict and Talbot: Carnegie Institution of Washington, D. C., publication 201, p. 167.

degree of malnutrition than the younger infants with which they are compared.

It has been recognized for some time that the heat production per kilogram of body weight is higher in the malnourished or marasmic

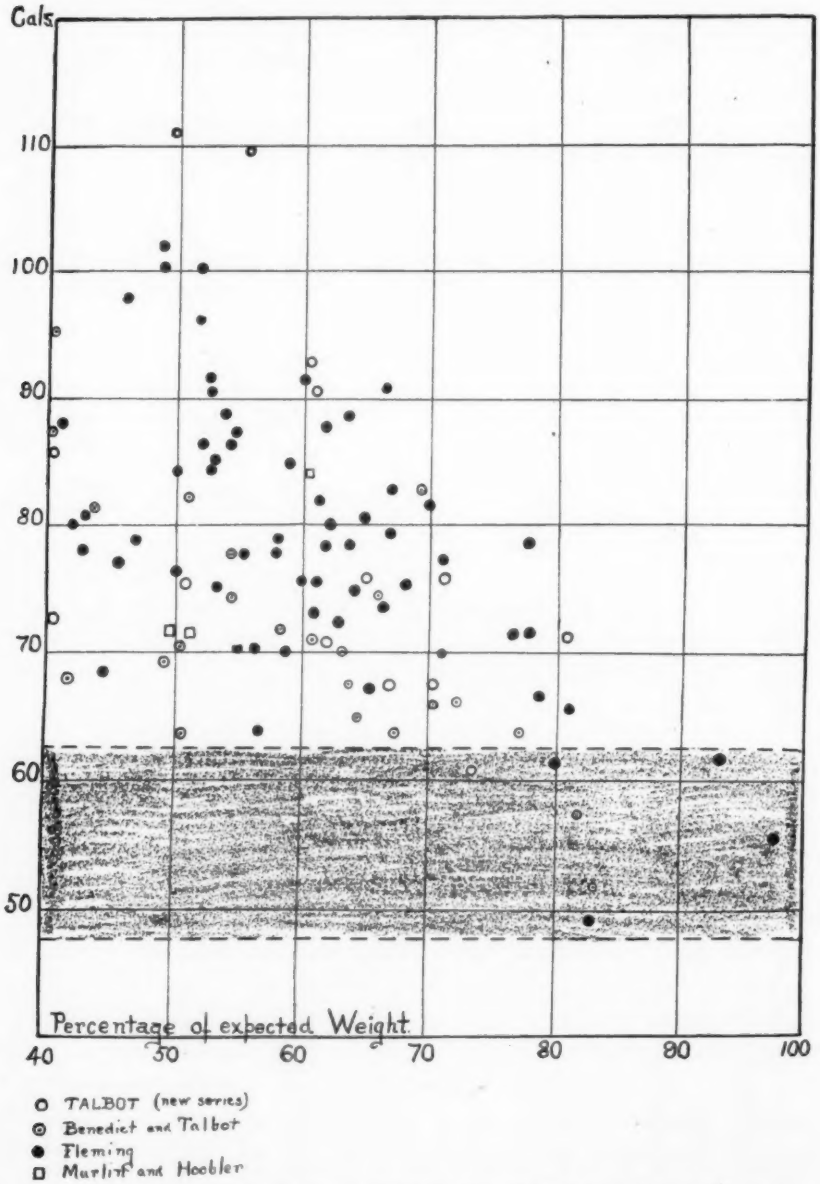

Fig 1.—Calories per kg. of actual weight: The shaded area shows the extreme limits of metabolism per kilogram of body weight of normal limits of body sexes at different ages. One hundred per cent. represents the average expected weight of the normal infant. The further the dots fall to the left the greater the case is underweight.

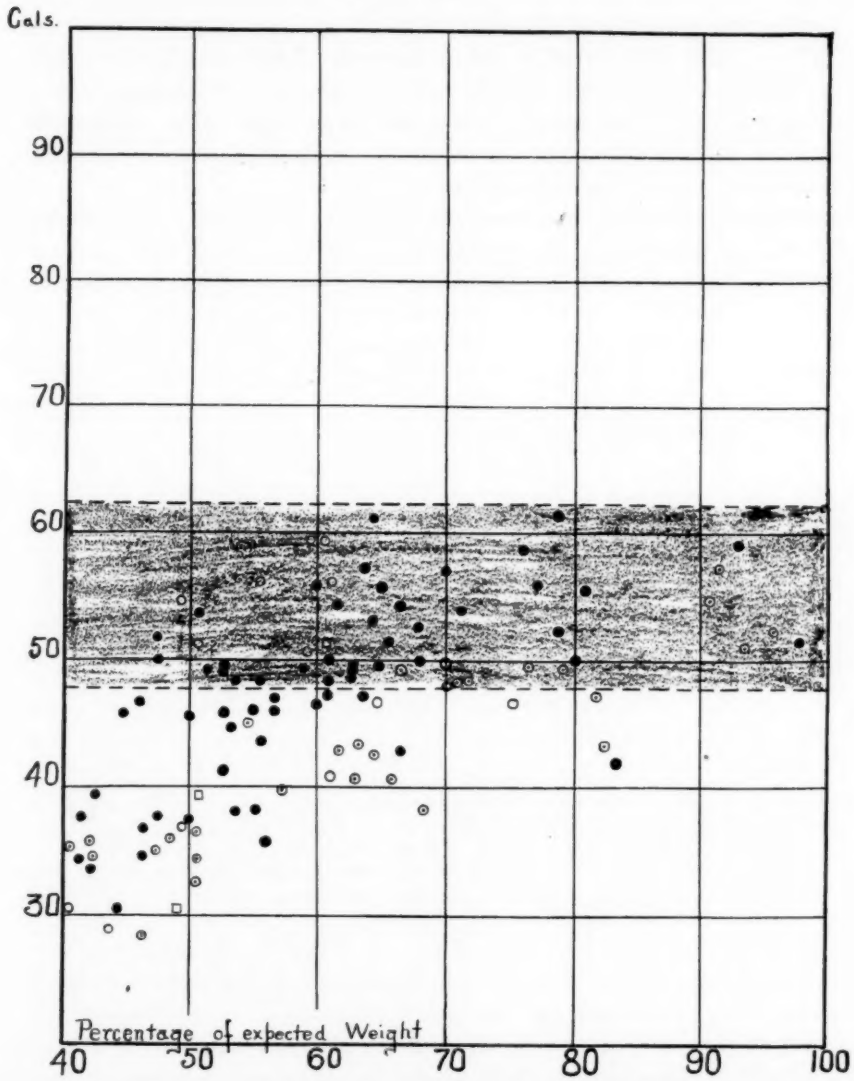

Fig. 2.—Calories per kg. of expected weight: The shaded area shows the normal variation as in Figure 1. The total calories of the infants plotted on this chart were divided by the expected weight of the infant, that is, the weight it would have attained if it had developed in a normal manner and had not shown any signs of malnutrition.

infant than in the normal infant. This is shown in Figure 1, the shaded area representing the variation of normal cases during infancy.[5]

Fleming[4] concluded from a study of his own and Benedict and Talbot's infants that until an infant becomes 35 per cent. under weight there is no fundamental change in the metabolism. Fleming's method of charting has been adopted here and to his cases have been added those of Howland,[6] Murlin and Hoobler,[3] and the new series of cases studied by me during the last two years.

Figure 1 shows that the metabolism of these cases falls outside of the average 10 per cent. limits when infants are 20 per cent. or more below the average weight, and indicates that the metabolism is

TABLE 3.—COMPOSITION OF INFANT'S BODY COMPILED FROM VARIOUS AUTHORS

Author	Condition	Age, Mos.	Wt., Gm.	Total in Grams					In 100 Parts of Fresh Substance				
				Water	Dry Substance	Fat: Ether Extract	Ash	Nitrogen	Water	Dry Substance	Fat: Ether Extract	Ash	Nitrogen
Camerer and Soldner[1]	Normal newborn	†	2,821	2,026.0	796.0	348.9	75.0	55.8	71.8	28.2	12.3	2.70	1.98
Sommerfeld[2]	Normal infant	3	4,340	3,053.0	1,287.0	568.9	118.7	98.7	70.15	29.85	13.4	2.73	2.27
Steinitz:													
Case 2[3]	Atrophic	3	2,625	2,098.2	526.8	37.9	86.0	50.9	79.9	20.1	1.45	2.73	2.32
Case 3	Atrophic	2½	1,960	1,612.4	347.6	35.9	62.7	41.7	82.3	17.7	1.80	3.20	2.13
Case 4	Atrophic	3¾	3,190	2,547.8	642.2	63.6	106.7	80.0	79.9	20.1	1.99	3.34	2.51
Steinitz & Weigert[4] *	Fat infant	4	3,711	2,187.3	1,523.7	897.7	110.7	83.6	58.94	41.06	24.17	2.98	2.25

1. Comerer and Soldner: Ztschr. f. Biol. **43**: 1, 1902.
2. Sommerfeld: Arch. f. Kinderh. **30**: 253, 1900.
3. Steinitz: Jahrb. f. Kinderh. **59**: 447, 1904.
4. Steinitz and Weigert: Beitr. z. chem. Physiol. u. Path. (Hofmeister's) **6**: 205, 1905.

* This child had been fed by its mother on gruels containing a large preponderance of carbohydrates.

† Average of six infants at term.

influenced by a less degree of malnutrition than was shown on Fleming's charts. It must be said, however, that he did not have normal figures with which to compare his "atrophic" infants.

This chart also shows that the more an infant is under the average weight the more calories it produces per kilogram of body weight. This would seem to suggest that body fat is an inert substance and that the high metabolism per unit of body weight is due, in a large part, to a loss of body fat.

If body fat is an inert substance and the loss of weight of these infants represents a loss of fat, then one would expect that if the

5. Benedict and Talbot: Carnegie Institution of Washington, D. C., Publication 302.

6. Howland: Trans. 15th Internat. Cong. on Hygiene & Demog. **2**:438, 1913.

metabolism were charted for calories per kilogram of expected weight instead of for calories per kilogram of true weight, it would be the same as if the lost fat were put back on the body and would approximate that of normal infants. This has been plotted in Figure 2. Normal variations are included in the shaded area between the dotted lines, and the calories per kilogram of the expected weight of the cases of malnutrition indicated by dots, squares and circles.

This chart shows that a much larger proportion of the infants fall within the average limits than in Figure 1 and seems to indicate that the high metabolism per kilogram of body weight shown in Figure 1 was due, in large part, to the absence of fat from the body. If fat does not take an active part in heat production, it means that those cases that fall within the dotted lines have lost body fat.

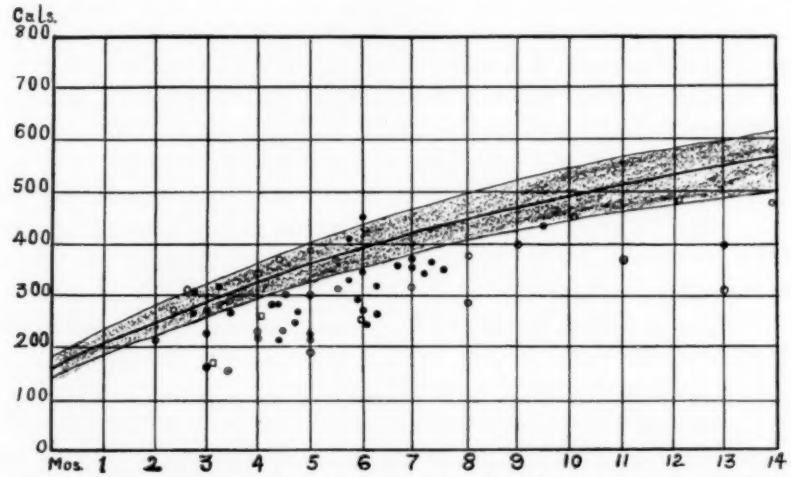

Fig. 3.—Total calories referred to age: The shaded area represents variations of the total metabolism of normal infants at different ages.

There is only fragmentary evidence on the composition of the body of normal and malnourished or "atrophic" infants. This is given in Table 3.

Table 3 shows that the greater the weight the more nitrogenous material there is in the body. On the other hand, there is very little difference between the percentage of nitrogen in the different cases. Moulton [7] has shown that cattle have a nitrogen content almost exactly proportional to the surface area. If the active protoplasmic tissue is represented principally by the nitrogen containing substances [8] one would expect that the total heat output would increase with the actual weight of the infant (Fig. 4), and that the heat output per kilogram

7. Moulton: J. Biol. Chem. **24**:299, 1916.
8. Lusk: Science of Nutrition, Ed. 3, Philadelphia and London, 1917, p. 130.

of the "expected weight" (the weight the infant would have achieved if it had gained normally and had the normal amount of body fat), would fall within normal limits. This is what happened in the majority of instances shown in Figure 2.

Murlin and Hoobler [3] did not consider that there was enough difference in the percentage composition of the body in fat, as given in the above table, to explain the difference in the heat production per kilo of body weight. The difference, however, is greater than it appears because the total amount of fat in the body of the normal infant is nearly ten times as great as in the so-called "atrophic" infants. The difference would be even greater if really fat infants, such as Benedict and Talbot's Case 129 [5] had been examined. For example, Sommerfeld's so-called "normal infant" of 3 months weighed 4,340 gm., while the weight of the average normal infant of that age is approximately 5,600 gm. His infant, therefore, was at least 20 per cent. below the expected weight for the age and, consequently, was not an "average normal" infant. It weighed about 40 per cent. less than Benedict and Talbot's Case 129 which was a fat normal infant of the same age, and weighed 7 kilos. Fleming thought that "owing to the loss of fat the insulation of the body was not efficient" but it seems to me that in the group of cases in which the metabolism per expected weight fell within normal limits, the body fat merely serves as a diluent of the metabolism. In the group of cases which fell below the average the lack of the insulating subcutaneous fat must play a part in modifying the metabolism.

Reference to Figure 2 shows that there is a group of cases that have a low metabolism per expected weight; the cases with the greatest degree of malnutrition apparently having the most abnormal metabolism. This finding is rather difficult to explain but allows of two explanations:

1. Because of the malnutrition there was a diminished amount of active protoplasmic tissue to make heat, or

2. There is a normal amount of protoplasmic tissue but because of the malnutrition, or some concomitant factor, the heat forming tissues are incapable of making the same amount of heat as during health. The composition of the body shows little or no difference between the percentage of nitrogen in well nourished fat infants, thin infants, or markedly malnourished infants and it may be assumed that the proportion of protein tissue in malnutrition is not abnormal. Before this can be accepted, however, further investigation is necessary. If the protein tissue is the only active tissue involved it would then seem that it was not functioning to the same degree in making heat in severe malnutrition as in health. Indeed the weakness of many malnourished infants and the difficulties to be surmounted in keeping

their body temperature normal is common experience with all clinicians. The evidence in Table 3 is against there being a qualitative diminution of the "active protoplasmic mass" and it may be assumed that the first possibility is ruled out. The second possibility conforms with clinical experience and may be taken as the more plausible explanation. It is conceivable that when the metabolism becomes so depressed that the

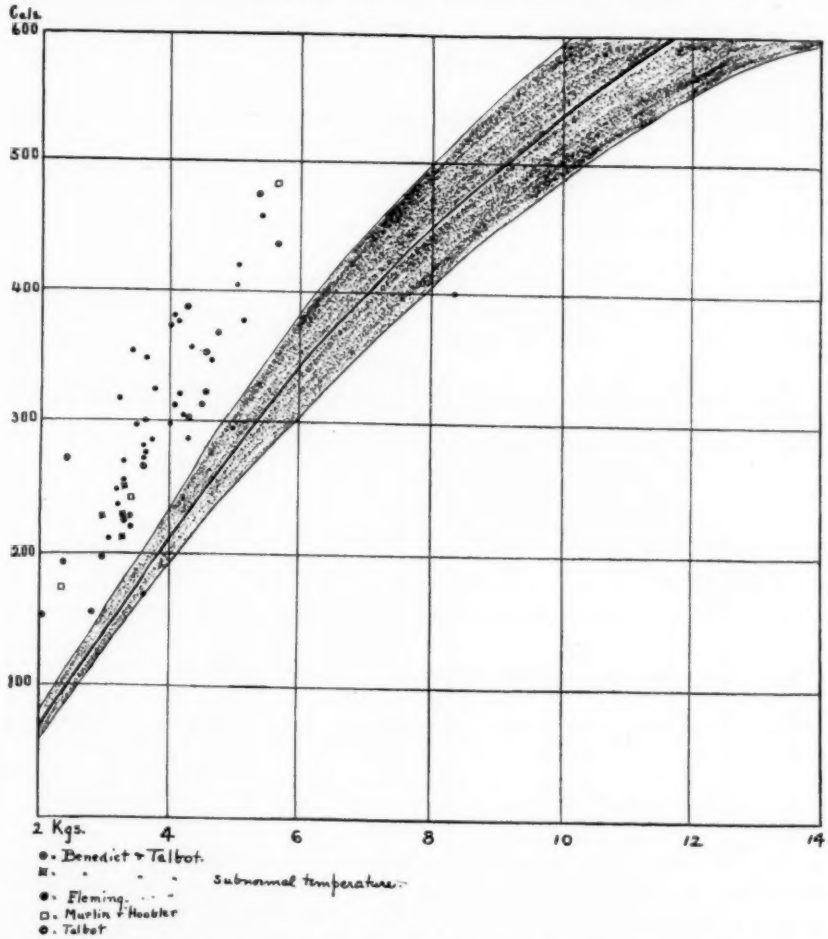

Fig. 4.—Total calories referred to weight: The shaded area represents the normal variation of the total metabolism of normal infants referred to weight. Benedict and Talbot found that when the total metabolism of normal infants was referred to weight there was less variation from the curve than in any other method of studying the cases.

normal temperature cannot be maintained except by external application of heat, these infants have entered into the same category as the cold blooded animal, the level of whose metabolism is determined in general by the surrounding temperature.

Figure 3 shows the level of the total metabolism at different ages compared to the normal.

In Figure 3 the total calories per age of normal infants is designated by a heavy line, with the 10 per cent. deviation, and shows that these cases of malnutrition produce fewer total calories than do average normal infants of the same age. A reasonable explanation of this may be found in Table 3 which shows that the total amount of nitrogenous tissue is, in general, dependent on the body weight.

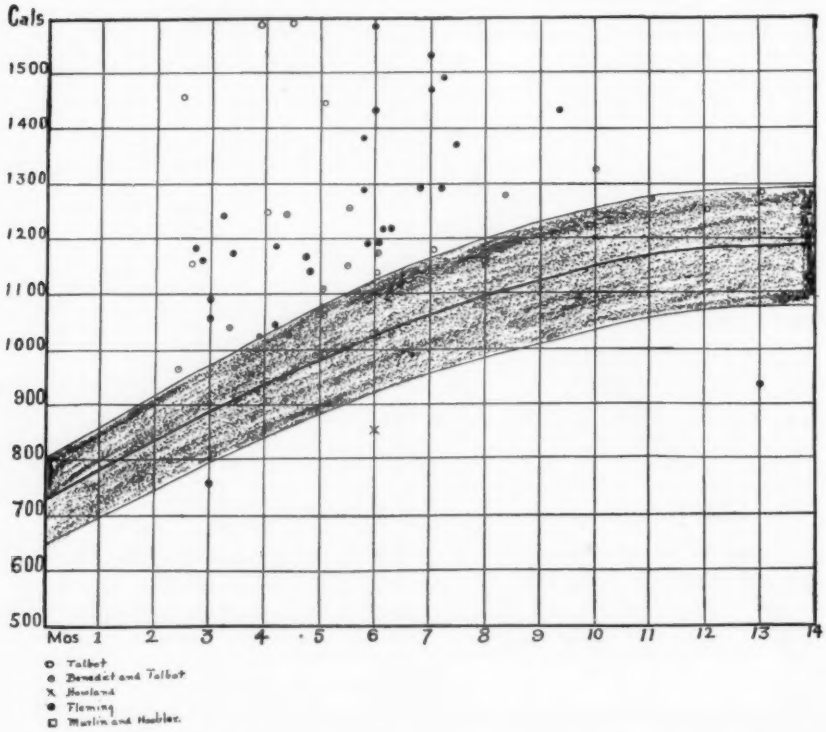

Fig. 5.—Total calories per square meter referred to age: The shaded area represents the normal variation of the total metabolism of normal infants per square meter referred to age.

In Figures 4, 5 and 6 the total calories referred to weight, the calories per square meter of body surface referred to age, and the calories per square meter of body surface referred to weight of infants with severe malnutrition are compared with average normal infants, the latter being represented by the normal curves. A comparison of the calories per square meter of body surface referred to body surface is not plotted since it gives a picture similar to that in Figures 4, 5 and 6.

Deductions may be drawn from these charts similar to those from Figure 1. On the other hand, other factors must play a part in increasing the metabolism above the normal range, especially the total metabolism per weight which is elevated and shows a similar picture to that in Figures 4, 5 and 6. Benedict and Talbot [5] found the metabolism to be very constant in normal individuals, and deviation from the normal in this respect is all the more significant. These charts also seem to show that a heat production greater than the normal is necessary to maintain the body temperature of these infants with malnutri-

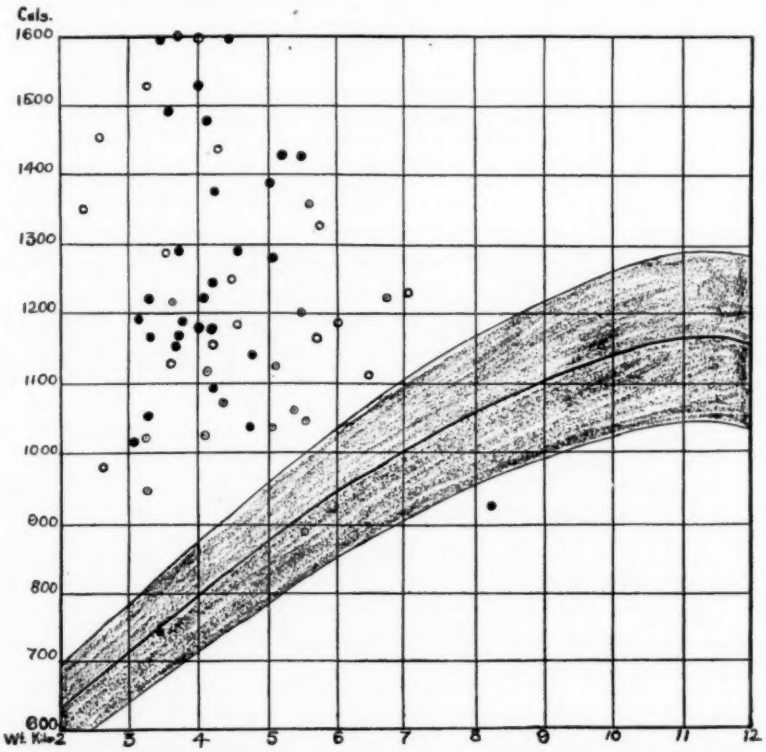

Fig. 6.—Calories per square meter referred to weight: The shaded area represents the normal variation of the total metabolism of normal infants per square meter referred to weight.

tion because of a relatively increased body surface and absence of the "protective" (Lusk), or "insulating" (Fleming) covering of subcutaneous fat.

Although no accurate measurements are available to prove that there is a relative increase in body surface as compared to weight in infants with malnutrition, there are many clinical records of reputable observers which show that the skin in severe malnutrition hangs in folds from the shrunken body. This is evidence that there is a relative

increase in the radiating surface of the body. It is also a well known clinical fact that it is very difficult to keep such infants warm. It is reasonable to suppose that if there is a relatively greater heat loss, nature will attempt to counteract this by a greater heat production. On the other hand, it is not my purpose now to argue that there is any casual relation between body surface and the metabolism of normal infants.

Table 4 from Klose [9] shows that the layer of subcutaneous fat tends to be diminished in severe malnutrition, and with the loss of body fat there is a loss of insulation, as suggested by Fleming, resulting in a greater heat loss from the surface.

TABLE 4.—Composition of the Skin of Infants Including Subcutaneous Tissue. (Klose)

No.	Diagnosis	Age	Length, Cm.	Weight, Gm.	Average Weight for Age (Holt), Gm.	Fat Content of Skin, per Cent.	In 100 Parts of Fat-free Skin	
							Water	Ash
1	Normal new-born	.....	.....	3,210	3,409	47.7	81.37	0.771
2	Premature; purulent peritonitis; sclerema	10 da.	44½	1,920	3,500	12.5	86.1	0.658
3	"Intoxication"	16 da.	50	2,610	3,500	46.3	76.3	0.690
4	"Mehlnährschaden"; edema	4 wk.	49	3,090	3,860	0.5	92.5	0.631
5	"Intoxication"	6 wk.	51	2,750	4,215	50.2	72.5	0.501
6	"Intoxication"; sclerema	7 wk.	51	3,150	4,443	49.8	79.9	0.284
7	Chronic "atrophy"	7 wk.	51	2,700	4,443	1.4	81.1	0.522
8	Parenteral indigestion (pertussis); bronchopneumonia	7 wk.	49½	2,220	4,443	0.9	77.5	0.838
9	Intoxication	8 wk.	52½	3,560	4,770	40.2	77.0	0.425
10	Chronic indigestion; acute enteritis	2 mo.	.....	3,030	4,770	3.0	83 8	0.357
11	"Atrophy"	2 mo.	43	2,100	4,770	8.3	72.8	0.969
12	Mehlnährschaden (pleuritis)	2½ mo.	49	2,230	5,165	46.2	78.5	0.561
13	Severe parenteral indigestion (pneumonia)	2½ mo.	57	3,400	5,165	28.3	75.7	0.823
14	Intoxication	2¾ mo.	54	3,220	5,363	34.7	75.3	0.365
15	Chronic "atrophy"	3 mo.	.....	2,670	5,560	1.0	82.5	0.326
16	"Atrophy"; sclerema	4 mo.	54	3,000	6,250	0.1	85.0	0.614
17	Intoxication	6 mo.	61	3,530	7,270	42.5	77.6	0.457
18	Intoxication	6½ mo.	.....	3,980	7,499	1.2	70.8	1.269
19	Bronchopneumonia; tetany	6½ mo.	59	4,000	7,499	47.5	79.4	0.536
20	Mehlnährschaden	7½ mo.	58	3,450	7,901	0.5	90.9	0.776
21	Sudden death; healthy infant	1½ yr.	82	9,595	110	62.0	74.0	1.129

The theory that the subcutaneous fat on the body acts as a protective covering and conserves body heat is not a new one as it has long been known that people living in cold climates, such as Esquimaux tend to be fat. Rubner, cited by Lusk [10] showed that the metabolism per kilo of the same dog when thin and when fat showed changes which indicated that "the presence of adipose tissue acts in the same way as does a warm fur to extend the range of the physical regulation, and to delay the onset of the chemical regulation of body temperature." (Lusk).

In Table 4 it is shown that in cases of severe infantile malnutrition ("atrophy") the subcutaneous fat is nearly absent. When the protective

9. Klose: Jahrb. f. Kinderh. **91**:(der dritten folge 41) 157, 1926
10. Rubner: Die Gesetze des Energieverbrauchs, 1902, p. 137.

covering of subcutaneous fat is lost, heat may be more easily lost from the body. This, together with the relatively greater surface area of radiation, facilitates heat loss. It is reasonable, then, to conclude that as long as the body is able, it responds to the demand put on it and produces extra heat, and, unless the indigestion, which is primarily responsible for the malnutrition, is not cured, the heat loss will eventually exceed the heat production and a subnormal temperature results. This has been seen clinically in cases in which the body temperature has not been brought back to normal by the application of external heat and the infant died.

Figure 2 showed that infants with the most severe malnutrition produce less heat per kilo of the expected heat than normal infants. These infants also tend to have a subnormal temperature and it seems logical to conclude that in cases of extreme malnutrition a stage is reached where the active protoplasmic tissue is no longer able to produce the required amount of heat. This may be a physiologic change due to the malnutrition or to the subnormal temperature. It is well known that in cases of severe infantile malnutrition as well as in premature infants, the digestion and absorption is poor as long as the temperature remains subnormal, and that with the application of external heat the digestion usually improves.

SUMMARY

There is no appreciable change in the metabolism of cases with severe malnutrition until there is a loss of 20 per cent. in the body weight. Beyond this point there is presumably a loss of subcutaneous fat and a larger body surface in relation to the body weight. With increasing malnutrition the divergence from the normal becomes greater and body heat is lost more easily because of the lack of the insulating layer of subcutaneous fat and of the greater radiation of heat due to the relative increase in body surface as compared to the weight. When the heat loss becomes greater than the heat production the temperature becomes subnormal. This condition can only be remedied by the application of enough external heat to make up for the loss. The basal metabolism per kilo of body weight is higher in infants with severe malnutrition than in normal average infants, being higher the greater the degree of malnutrition.

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THE FOOD REQUIREMENTS OF CHILDREN

II—PROTEIN REQUIREMENT *

L. EMMETT HOLT, M.D. AND HELEN L. FALES

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In the first paper of the series on the food requirements of children the total caloric need throughout the entire period of growth was discussed in detail. The next step in the consideration of food needs is a study of the distribution of the total calories necessary. This involves the estimation of the required amounts of fat, carbohydrate and protein to be supplied in the daily diet and the relative proportions of each of these. When the total caloric need is known the proportion of the different constituents is most concisely expressed by the percentage of fat, carbohydrate and protein which are given.

All three of these nutritive substances are sources of energy. There are, however, other important considerations which affect the amount of each one of them in the diet. Especially is this true of the protein. Before considering the other food elements, it is necessary, first, to establish the protein requirement. Proteins differ greatly in their composition and it is impossible to consider the total protein requirement without taking these differences into account.

As is well known, the food proteins are composed of fifteen or twenty amino-acids which are combined in varying proportions in the different proteins. In the intestines, the food proteins are split up into amino-acids which are then absorbed and subsequently recombined to form the proteins of the body. The proportions of amino-acids in the body protein are not the same as in the food proteins. As a consequence, not all the amino-acids of the food are utilized in building up or repairing the body structure. Those amino-acids which are not utilized as building materials are used largely for energy, being broken down into urea and excreted in the urine. A food protein may furnish a considerable excess of one or more of the amino-acids needed as building material, while at the same time it may be deficient in other necessary amino-acids. Certain of the amino-acids, such as leucin, glutamic acid, arginin, prolin, etc., which form large proportions of the body proteins, are present in abundance in all food proteins; consequently an ample supply of these is always assured. Other amino-acids which are especially needed in growth, such as lysin, cystin, trypto-

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phan, etc., are found in much smaller and in widely varying proportions in the different food proteins. Many of the proteins are in fact entirely wanting in one or another of these amino-acids. Hence, special care must be taken to provide in the diet of growing children either the proteins having the larger proportion of these important amino-acids or else there must be furnished a greatly increased supply of the proteins which have the lower proportions of these substances.

It is obvious that the total protein requirement for children during the period of growth is to a great extent dependent on the character of the protein given. The animal proteins approximate more nearly the proteins of the human body than do those of vegetable origin and for this reason are preferable. For the growing child, therefore, the animal proteins, such as are furnished in milk, eggs and meat, are distinctly of a higher grade than the vegetable proteins. It is possible that when the knowledge of the structure of the body proteins has progressed further a combination of vegetable proteins might be made to approximate for nutritive purposes the quality of animal protein. With our present knowledge, however, it appears necessary if vegetable proteins are depended on to supply them in large amounts, in order to insure normal growth.

In estimating the child's protein need two functions of protein must be considered. The first is the requirement for tissue repair and general maintenance; the second is that for growth. In adult life the first need is the only one to be supplied. In childhood the second is equally important. Even the protein requirement of the adult has been the subject of much controversy. It has been found possible to maintain nitrogen equilibrium in an adult man or woman on a protein intake as low as 40 gm. daily. Some writers believe that this minimum allowance is a sufficient supply. The average adult dietary, however, as compiled from many sources, contains from 100 to 120 gm. protein daily. This naturally adjusted intake has been regarded by many as an expression of the optimum. This amount of protein allows an average of about 1.4 gm. protein per kilo of body weight.

Sherman[1] recently found the average protein minimum in 109 adults to be 44.4 gm. daily. This represents 0.635 gm. per kilo for a person of average weight. He concludes that in an adult 1.0 gm. protein per kilo is an ample allowance for maintenance. The work of various investigators indicates that the entire need for maintenance can probably be supplied by vegetable protein. Sherman, however, believes that better results are obtained by supplying part of the maintenance requirement by animal protein. Among the vegetable proteins certain ones, especially zein—the protein of corn—are insufficient even for maintenance.

1. Sherman, H. C.: J. Biol. Chem. **41**:97, 1920.

From the knowledge of the adult protein need it may reasonably be inferred that the growing child requires for maintenance from 1.0 to 1.5 gm. per kilo of body weight daily. It is probable that this can be supplied either from vegetable or animal sources. In addition to the maintenance need, however, the child must be supplied with a generous amount of protein for growth. Because the vegetable proteins as a group are so poor in certain of the important amino acids it seems desirable and probably necessary to supply the growth need by animal protein. How much protein should be furnished to cover this requirement is difficult to estimate.

No experimental work has been reported on the protein need of children and the effect on their growth of either a very low or very generous protein intake. Osborne and Mendel [2] have been able to obtain quantitative results on protein needs in their work with rats. They have determined exactly how much of certain proteins will support normal growth in rats and also to what extent the amount of these proteins in the diet can be reduced if their quality is improved by the addition of certain amino acids in which they are known to be deficient. Such experimentation is by its very nature quite impossible with children. Accordingly, about the only guide to a knowledge of the total protein need of children is found in a study of the actual amounts of protein taken by normal healthy children in their customary diet. We fully realize that the results of this method of investigation are not conclusive, but they are strongly suggestive. They, therefore, deserve careful consideration until further light is shed on the question by more extended observations, possibly different in character.

The protein intake of the normal nursing infant is very low. It ranges during the first nine months of life approximately from 8.0 to 12.0 gm daily. This is equivalent to only about 1.5 gm. per kilo. Up to the age of 8 or 9 months the protein taken by the nursing infant seldom exceeds 12 gm. daily. This amount must be sufficient to supply not only the maintenance need but the need for growth during the most active period of growth in the life of the child, for we find our best examples of good nutrition and growth in the breast-fed infants. The reason for the adequacy of this small protein intake is that the protein of woman's milk is certainly best adapted in its amino acid composition for digestion and assimilation by the infant.

When cow's milk is substituted for woman's milk experience has shown that the protein intake must be considerably increased—doubled or even trebled. Infants from 1 month to 9 months of age receive from 15 to 30 gm. protein daily when fed on the usual modification of cow's milk. This represents fully 3.0 gm. protein and often 4.0 gm.

2. Osborne, T. B., and Mendel, L. F.: J. Biol. Chem. **25**:1, 1916, id. **37**:223, 1919, and others.

protein per kilo. The increase in protein requirement when cow's milk is substituted for woman's milk is probably due to the difference between the two milks in amino-acid content. Woman's milk contains about twice as much lactalbumin as does cow's milk. The work of Mendel and Osborne, as well as that of others, has shown that lactalbumin is especially efficient in promoting growth, while casein, which forms five-sixths of the protein of cow's milk, is of comparatively low grade as a growth protein, being notably deficient in cystine. Furthermore, lactalbumin, which forms two-thirds of the protein of woman's milk, contains of all the proteins the highest proportions of the amino acids leucini, lysin and tryptophan.

The failure of condensed milk as a food for infants has been ascribed to its low fat and its relatively high sugar content. It now seems clear that equally imporant—probably more important than either of these—is its low protein. As usually fed in dilutions of one to eight or one to six, the protein ranges from 1.0 to 1.4 per cent., which is only about that of woman's milk.

Again, in the early days of milk modification by the percentage method it was thought that cow's milk mixtures in which the proportions of fat, sugar and protein were as nearly as possible those found in woman's milk would be the best substitute for it. The many failures from the use of such formulas have been attributed to the too high fat, but it now seems quite evident that the low protein was even more at fault. It has become increasingly clear with clinical experience that the majority of infants will not thrive normally on cow's milk unless they are given two or three times as much protein as is contained in woman's milk.

The proportion of vegetable proteins in the diet of infants is a very small one. Whether nursed or artificially fed the infant receives practically his entire protein supply in the form of animal protein at least during the first six months of life. It is only when cereal additions are given, either as flour incorporated in the milk formula or as cereal given separately, that a portion, although at first a very small one, of the protein given is of vegetable origin.

Very little attention has thus far been paid to the quantitative composition of the diet of children over 1 year of age. There is, therefore, very little material in the literature concerning the actual daily amount of protein taken by older children. The few scattered data published are for the most part incidental to researches on other subjects. Most of the authors whose reports on the total calories taken by children were discussed in the first paper of our series have also reported the protein content of the diets taken.

Gillett [3] has compiled from eighteen authors 146 cases, including most of the values for protein intake given in the literature up to 1917, and has summarized them in her article. This summary is shown in Table 1. It will be seen that in all the groups the average intake was at least 2 gm. protein per kilo and that the younger children took on the average 3 gm. per kilo.

TABLE 1.—SUMMARY OF LITERATURE ON PROTEIN INTAKE PER KILO (GILLETT)

Age, Years	Number of Cases	Total Protein, Gm. Daily	Protein Intake, Average Gm. per K.
2– 5	51	53	3.3
6– 9	44	67	2.6
10–13	33	73	2.0
14–17	18	94	2.2

Total range in all cases over one year, 1.37–4.86.

Müller,[4] whose cases are included in Gillett's summary, discusses in considerable detail the protein intake of the thirty-two children studied by him. These children, from 1 to 6 years of age, took on the average 3.5 gm. protein per kilo daily It must be borne in mind, however, that these children were much underweight. Müller thinks that the protein need of children is proportionally very much greater than that of adults, and that no attempt should be made to reduce the protein intake to a minimum lest growth be interfered with and general nutrition impaired.

Gephart [5] in his observations on the adolescent boys in St. Paul's School found the protein intake to be very high. The average total daily protein was about 160 gm.; while the average protein per kilo ranged from 2.6 to 3.8 gm. per kilo. His averages are shown in Table 2.

TABLE 2.—AVERAGE PROTEIN INTAKE IN GEPHART'S OBSERVATIONS

	Average Age: Yrs.	Mos.	Total Protein, Gm. Daily	Protein Intake, Average Gm. per K.
Lower school	13	6	164	3.76
Middle school	14	7	165	3.26
Upper school	16	1	157	2.60

Camerer,[6] whose schedule for feeding older children has been widely followed, recommends over 4 gm. per kilo for the first year, from 3 to 4 up to the eighth year, over 2 gm. until the fourteenth year, diminishing to 1.7 gm. at the end of the growth period.

3. Gillett, Lucy H.: Publication 115, N. Y. Assn. for Imp. Cond. of Poor, 1917.
4. Müller, E.: Biochem. Ztschr. **5**:143, 1907.
5. Gephart, F. C.: Boston M. & S. J. **176**:17, 1917.
6. Camerer: Stoffwechsel des Kindes, 1896.

TABLE 3.—Average Protein Intake of the Children Studied

Age, Years	Boys					Girls					Both Sexes				
	Number of Cases	Total Protein, Gm. Daily	Protein per K.	Per Cent. Animal Protein	Per Cent. Vegetable Protein	Number of Cases	Total Protein, Gm. Daily	Protein per K.	Per Cent. Animal Protein	Per Cent. Vegetable Protein	Number of Cases	Total Protein, Gm. Daily	Protein per K.	Per Cent. Animal Protein	Per Cent. Vegetable Protein
1–2	2	32	3.2	75	25	5	49	4.4	70	30	7	44	4.1	71	29
2–3	4	48	3.4	71	29	7	56	4.1	72	28	11	53	3.9	71	29
3–4	6	51	3.8	71	29	4	68	4.4	68	32	10	58	4.0	70	30
4–5	7	57	3.3	70	30	5	53	3.0	70	30	12	56	3.2	70	30
5–6	5	63	3.3	70	30	5	58	3.3	64	36	10	60	3.3	67	33
6–7	4	76	3.0	63	57	4	50	2.5	68	32	8	60	2.7	67	33
7–8	2	69	2.7	56	44	3	66	2.7	59	41	5	67	2.6	58	42
8–9	4	80	3.1	71	29	5	75	2.7	70	30	9	78	2.9	70	30
9–10	5	88	3.0	63	37	4	68	2.5	68	32	9	80	2.8	64	36
10–11	6	107	3.5	69	31	3	73	2.2	64	36	9	96	3.1	68	32
11–12	3	82	2.2	64	36	1	77	2.1	73	27	4	80	2.2	64	36
12–13	1	87	1.9	59	41	2	73	1.6	69	31	3	78	1.7	65	35
13–14	..	...	...	..	..	1	74	1.7	60	40	1	74	1.7	60	40
14–15	2	162	3.4	63	37	1	66	1.4	57	43	3	130	2.4	63	37
15–16	2	134	2.4	67	33	1	111	2.1	64	36	3	130	2.3	65	35
16–17	1	116	2.2	56	45	..	...	...	..	..	1	116	2.2	56	45
17–18	..	...	...	..	..	1	115	2.0	82	18	1	115	2.0	82	18

In a former article we[7] presented the values for total calories taken by over one hundred healthy children from one to seventeen years of age. In each of these cases we obtained complete diet records for a period of four days. These children were from intelligent well-to-do families and may be assumed to be taking diets which are fairly representative of what children under such circumstances usually receive. A study of the amount of protein taken by these children should, therefore, give some idea of the usual amount in the diet of healthy children. The average values for the total protein, the protein per kilo and the proportion of animal and vegetable protein taken at different ages are given in Table 3. The average total protein in the second year was 44 gm., in the sixth and seventh year 60 gm., in the

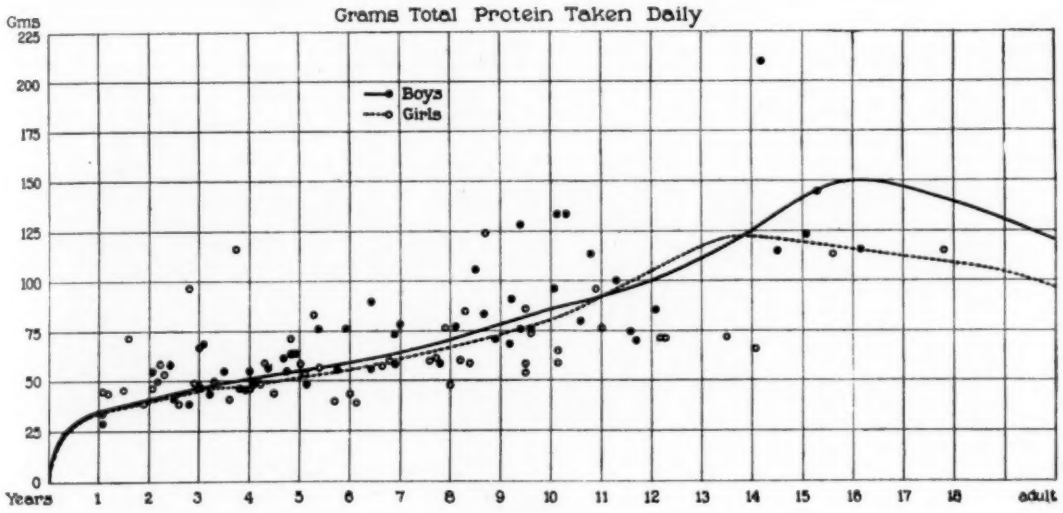

FIGURE 1

twelfth year 80 gm., in the fourteenth to the sixteenth year 130 gm. and in the eighteenth 115 gm.

Figure 1 shows the total daily intake of protein of the individual children. Our observations indicate that approximately 15 per cent. of the total calories taken by children over 1 year old should be supplied by protein. The solid and dotted lines represent for boys and girls the grams of protein which are equivalent to 15 per cent. of the calories recommended in our previous paper for the different ages. While the great majority of these cases fall reasonably near the average lines there are some notable exceptions. There are four girls whose protein intake was very high; three were between 18 months and 4 years of age and one was 8½ years old. All four were extremely

7. Holt, L. E., and Fales, H. L.: Am. J. Dis. Child. **21**:1, 1921.

active children in excellent health whose total food intake was very high. Two large girls of 13½ and 14 years, respectively, took a very low amount of protein. Both had attained practically their full growth, and for them really the only protein need was that for maintenance.

There were three boys about 10 years old with very high intake. The explanation in each case was excessive activity. A 14 year old boy taking 210 gm. protein daily is an example of what is so often observed, that is, the very large amount of food frequently taken by an active rapidly-growing boy at this age.

The values for grams of protein per kilo of body weight by these children are shown in Figure 2, the dots indicating the values for boys, the circles those for girls The solid and dotted lines represent the values for grams of protein per kilo equivalent to 15 per cent. of the

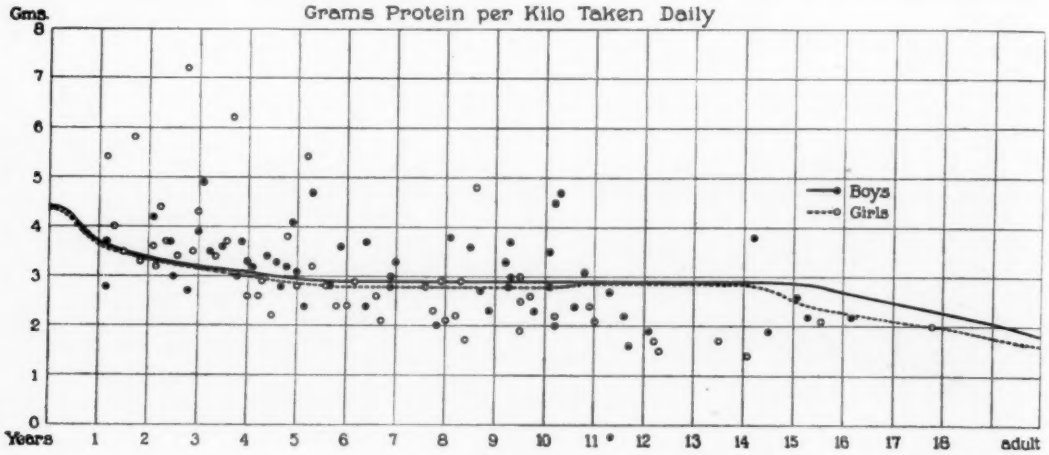

FIGURE 2

calories per kilo recommended for different ages in our previous paper. Four-fifths of all the children observed took between 2 and 4 gm. protein per kilo. Only nine took less than 2 gm. per kilo, all of these children being over 8 years of age. Fourteen took more than 4 gm. per kilo. These were mostly young and very active children, only four being 5 years of age. In general, the amount taken by the younger children was largest, the intake per kilo tending to diminish as age advanced.

It is seen that the protein intake of the children under 6 years average over 3 gm. per kilo. That of the older children averaged over 2 gm. per kilo for most years, there being a tendency to a reduction with the years. The values for girls between 12 and 15 are low, but there are too few observations to warrant deductions. It is probable that with more data the average protein intake of these years

would be higher than is shown in Table 3 since these are the years of most rapid growth and, as we have shown in the discussion of total caloric needs, the food requirements are very high during adolescence.

These observations on normal children have also been analyzed with respect to the proportion of animal and vegetable protein in the diets taken. Most of the children took over 60 per cent. of their total protein in the form of animal protein from milk, eggs, meat, etc. The average of all the cases show that 66 per cent. of the total protein was animal and 34 per cent vegetable protein. In only one instance did a child take less than half of his protein as animal protein. Figure 3 shows graphically the percentage division of the total protein in the diet of each child. The values are arranged in order of age.

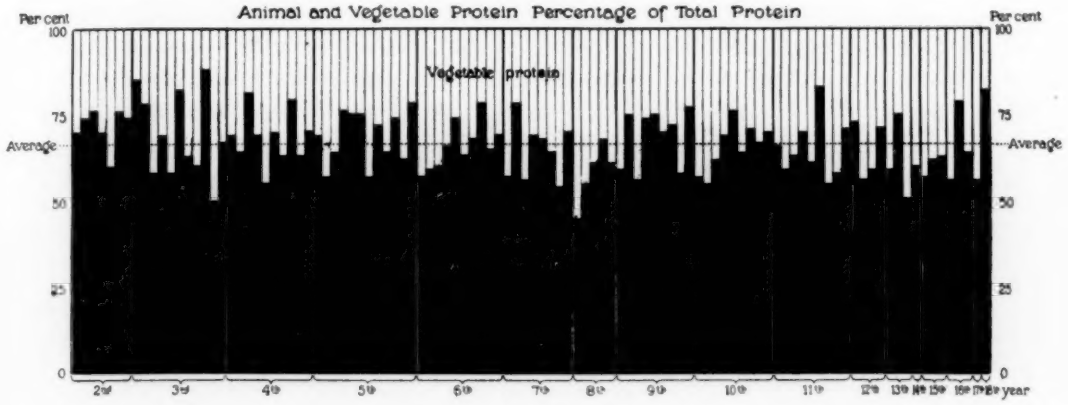

FIGURE 3

That there was found so little variation in the proportion of animal and vegetable protein in the different cases was to us a matter of much surprise. There are only three values for animal protein below 55 per cent. and only four above 80 per cent. of the total protein. Figure 3 shows clearly that there was no constant variation according to age. The older children received practically the same proportion of animal and vegetable proteins as did the younger ones.

From the foregoing observations it is seen that healthy children take in their usual diet about 4 gm. protein per kilo at the age of 1 year, the amount diminishing to about 2.6 gm. at 6 years of age and remaining at about this value or slightly below it until the end of growth. Of this total practically two-thirds is animal protein. Thus, there is in the usual diet about 2.7 gm. animal protein and 1.3 gm. vegetable protein at the age of 1 year and about 1.6 gm. animal protein and 1 gm. vegetable protein at the age of 6 years and thereafter. This

quantity of protein may, perhaps, be regarded as the optimum and may, therefore, be recommended as a suitable intake for the growing child.

It is quite possible that children might do well if a smaller proportion of the protein given were animal protein. However, from what is known of the growth properties of the vegetable proteins as a class it is evident that a much larger amount of vegetable protein would be required to furnish the amino acids necessary for normal growth. Vegetable protein cannot replace animal protein gram for gram but must be given in greater amounts. Accordingly, if it is desired to give a larger proportion of vegetable protein than the usual one-third of the total requirement the total protein intake must be considerably increased. When, however, the amount of vegetable protein given is increased very much above the average—that is, about 1 gm. per kilo—the amount of carbohydrate which must be necessarily taken with it, because of the nature of the occurrence of the vegetable protein is likely to be excessive and may be a menace to proper digestion.

SUMMARY

1. No estimates of the amount of protein required by growing children can be made without taking into account the kind of protein given, since the amino acid content of different proteins varies considerably.

2. In estimating the protein needs of the child not only must the need for maintenance be supplied, as with the adult, but also a liberal amount of protein must be allowed for growth.

3. Vegetable proteins as a class are of a distinctly lower grade than animal proteins. While they may be adequate for maintenance, with our present knowledge it is hazardous to depend on them for growth.

4. The fact that the small amount of protein taken by nursing infants is adequate for healthy growth is due to the superior amino acid composition of the proteins of woman's milk.

5. When cow's milk is substituted for woman's milk the amount of protein allowed should be doubled or trebled.

6. The average amount of protein taken in the usual mixed diet by over one hundred healthy children ranged from 44 gm. daily in the second year to 130 gm daily in the fifteenth year. The latter figure exceeds the average adult need and obviously should do so, since adults require protein for maintenance only.

7. The amount of protein per kilo of body weight taken by these children averaged about 4 gm. at one year, diminished to about 2.6 gm. at 6 years and remained at about this value until the end of growth.

8. The children studied by us took about two-thirds of their protein as animal protein and one-third as vegetable protein.

OBSERVATIONS ON THE CAPILLARIES OF THE NORMAL INFANT *

KATHERINE M. MAYER
CHICAGO

While seeking a method to determine the capillary blood pressure, Lombard [1] discovered that the circulation in the capillaries of the living person could be observed with a microscope. The skin was rendered transparent with either glycerin or cedar oil. Magnifications of from ten to twenty-five times were found best. For illumination he used either a Nernst lamp or daylight. Later Weiss [2] observed the capillaries of persons suffering from various diseases. In his method the electric light rays pass through a series of lenses before striking the area of skin to be illuminated; later, he used only one lense.[3] In determining capillary blood pressure, Danzer and Hooker [4] used merely a strong electric light and castor oil with their pressure apparatus and objective 3 and ocular 4 of the microscope.

The apparatus used to make my observations is very simple and not bulky. It consists of a small electric lamp (Fig. 1) with a strong convex lense made in the bulb.[5] The lamp is attached to the objective of the microscope by a metal attachment, in such a way that the light and the microscope can be focused on the same area. Objective 3 and ocular 2 were found best. The area to be observed is first cleaned with green soap, then with alcohol, and well dried before the glycerin or cedar oil is applied. The oil renders the skin transparent by penetrating the epidermis and so doing away with the light reflections from the uneven surface. In very young children, the oil can be applied directly without the preliminary cleaning. The third finger of the infant is strapped loosely, with a narrow strip of adhesive plaster to a wooden tongue depressor. With slight pressure on the knuckle the finger can be held quite firmly without interfering much with the circulation at the nail fold. Observations are made in the area about the middle of the nail fold. The infants were taken after the morning feeding, when they

* Received for publication, June 30, 1921.
* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.
* Read before the Chicago Pediatric Society, March 22, 1921.

1. Lombard, W. T.: Am. J. Physiol. **29**:335, 1912.
2. Weiss, E.: Deutsch. Arch. f. klin. Med. **119**:1, 1916.
3. Weiss, E.: Ztschr. f. Exper. Pathol. u. Therap. **19**:390, 1918.
4. Danzer, C. S., and Hooker, D. R.: Am. J. Physiol. **52**:136, 1920.
5. This lens was furnished by American Specialty Co.

would most likely sleep or be quiet. Needless to say, it is impossible to make observations when the child is irritable or very restless.

In 1892, Spalteholz [6] studied the distribution of the blood vessels in the skin by injecting the vessels with a colored gelatinous solution. Among his conclusions is the following statement:

> All the vessels which go to the papillae originate from the anastomizing vessels in the subcapillary plexus, and always in the form of small trunks, whose smallest branches run a short distance in the direction of the papillary rows, perpendicular under these, and run without further anastomoses and send their capillaries into the papillae. . . . (This coincides with my observations.) All arteries leading to the skin and their larger branches are the same in distribution and number in the new-born.

Fig. 1.—Microscope with lamp attached.

He makes no statement concerning the end capillaries of the skin in the new-born.

In 1919, Holland and Meyer [7] observed the capillaries in healthy normal children, and in those with exudative diathesis. They used the method described by Weiss. They describe and illustrate their findings in detail as follows:

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6. Spalteholz, W.: His Arch. f. Anat. u. Entwickelungsgesch. **1**: 1893.
7. Holland, M., and Meyer, L.: München. med. Wchnschr. **66**:1191, 1919.

In two-day old infants the end loops do not extend into the limbus (tissue between subcapillary plexus and skin surface), but remain in the region of the subcapillary plexus and extend up from there as short loops in the process of development. Arterial and venous limbs are clearly differentiated. Occasionally one finds a figure of eight loop. At one week regularity in distribution is seen. The short loops do not extend into the limbus. The venous limb is absolutely not differentiated from the arterial limb. (This differs from their findings at two days.) At four weeks the capillaries are of various widths, some are close together and with rich anastomosis, and some are more widely separated. Pronounced differences in length do not exist. The vessels project into the limbus.

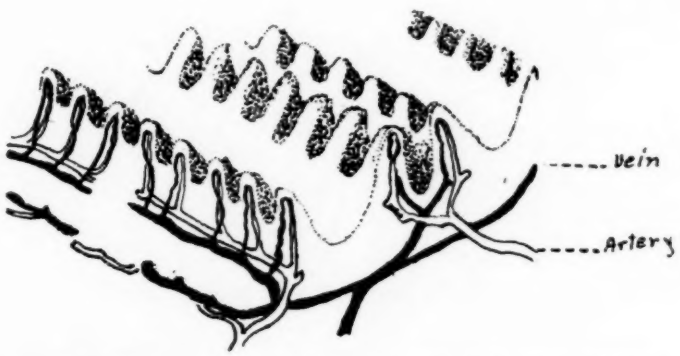

Fig. 2.—The uppermost part of the pars papillaris cutis without the epidermis (Spalteholz).

Fig. 3.—Normal infant, 2 days old.

They describe the picture in the normal young infant as follows:

The width of the capillaries is from 0.03 to 0.05 mm. and length 0.15 mm. Difference in length and variation in width is seldom found, and then the difference is not marked. Well marked serpentine forms are seldom found, but, as a whole, there is a tendency to greater irregularity and serpentine forms. The vessels run straight, but not exactly parallel. Markedly twisted loops are seldom found. The arterial and venous limbs are almost always

well differentiated. In almost all children, the subcapillary plexus is clearly seen. Anastomosis one seldom finds among the end capillaries, but the subcapillary plexus is rich in anastomosis.

Later, Mertz [8] published his observations. He divides his results into three groups; first, comprising the children from 1 to 3 months of age; second, from 4 to 6 months, and third, those over 6 months.

In the first four or six weeks the loops are very short and project up from the ground substance into the limbus, more as broad bow shaped protrusions than as short loops. It is only the distal part of these loops that one can term the capillary loops. After several weeks there is found a better develop-

Fig. 4.—Normal infant, 7 days old.

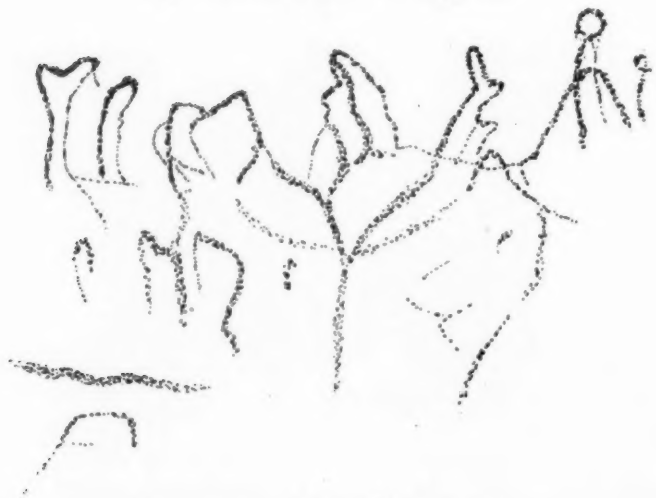

Fig. 5.—Normal infant, 3 weeks old.

ment of the capillaries and an extension into the skin along the edge of the nail fold. The age when this definite development occurs seems dependent on the development of the child. In the first three months, the capillary loops are from 20 to 60 microns long, are relatively not close together and anastomosis is seldom seen. In the following period, from 3 to 6 months, there is a rapid lengthening of the loops; they reach 200 microns. The loops are closer together and have greater anastomosis than before.

8. Mertz, A.: Monatschr. f. Kinderh. **18**:13, 1920.

He describes a variation in length of the capillaries of children of the same age and in the same child on different fingers, this being related to the length of the nail fold; if it is pushed back, the loops are shorter than if it is grown further out over the nail.

My observations were made on infants at the Children's Memorial Hospital and at St. Vincent's Orphan Asylum. Only those infants were examined who appeared to be in good condition. No child with

Fig. 6.—Normal infant, 5 weeks old.

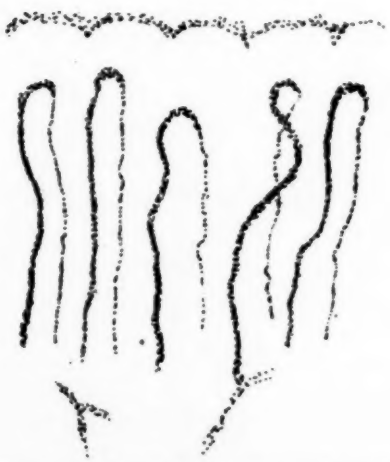

Fig. 7.—Normal infant, 9 months old.

an infection, however slight, with eczema, or in poor physical development was taken as a normal child. Many infants could not be observed as they became too irritable when an attempt was made to hold the hand absolutely quiet under the objective of the microscope. It was found most satisfactory to hold the infant in a sitting position in such a way that the hand could rest comfortably on the stage of the micro-

scope. Often the infant slept quietly during an entire observation. Drawings were made of those infants who held absolutely quiet for a relatively long time.

In infants 1 or 2 days old (Fig. 3) the capillaries appear as a fine network plexus lying close to the skin surface. This plexus can be seen extending back from the edge of the nail fold for quite a distance. Only the most distal vessels of this plexus can be called end capillaries. These are bow shaped, vary in length and height, and the arterial and the venous limbs can be differentiated. The arterial limb is hairlike

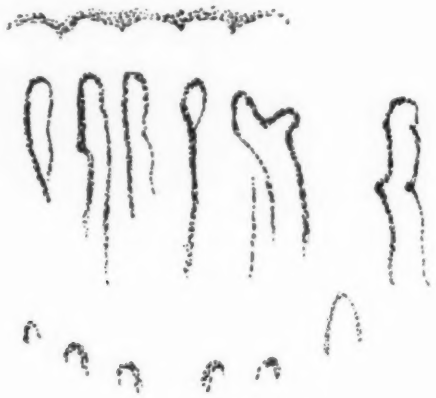

Fig. 8.—Normal adult.

Fig. 9.—Child with malnutrition, 10 weeks old.

and broadens gradually into the venous limb. There is no regularity in the distribution of these loops along the plexus margin. Occasionally, there is a short narrow loop. There is no anastomosis except in the subcapillary plexus.

At one week (Fig. 4) the capillaries begin to elongate and project out into the tissue between the plexus and the skin surface. In some the loops appear triangular, the angle appearing at the top and the base remaining broad. Other loops may be somewhat square. The

capillaries begin to appear more loop than bow shaped and they are slightly more regular in their distribution. There is no anastomosis between these and loops. When such seemed to be present it was found upon focusing that one loop was superimposed on another. The arterial and venous limbs are clearly differentiated.

At three weeks (Fig. 5) the loops are definitely formed and are separate from each other at relatively equal distances, one loop extending into each papilla. The loops vary in length and breadth, many loops being still quite broad and short. No anastomosis occurs except in the subcapillary plexus, that is, the vessels at the base of the loops. The arterial limb of the capillary vessel is hairlike and broadens out into the venous limb before turning back on itself. The venous limb often is slightly tortuous. The apparent anastomosis in Figure 6 was found to be superimposed vessels in which the two limbs were not in the same plane. There is little if any variation in the caliber of the different vessels.

At two months the capillaries are longer and the distance between the subcapillary plexus and the skin surface is also greater. The vessels disappear in the plexus, which appears as a pinkish haze with here and there a deeper red line, representing either a larger vessel or one closer to the surface.

At about three months, the capillaries are well formed; they are longer than those at two months. There are some spiral and figure of 8 shaped vessels. As the capillaries increase in length, they appear much closer together. From three months on the vessels increase in length until the long narrow loops of the adult type (Fig. 8) are reached. The subcapillary plexus shows less anastomosis at the base of the loops.

In general, it might be said that from birth the end capillaries begin development from small loops at the periphery of the subcapillary plexus. Until about the third month the development is very rapid. From then on there is not much change.

I wish to thank Dr. Samuel Amberg for his direction in this work.

CLINICAL INVESTIGATIONS ON ORTHOSTATIC ALBUMINURIA*

HIDEO SAITO, M.D.
NAGASAKI, JAPAN

Although orthostatic albuminuria has been the subject of frequent investigation, the pathology of the condition is far from being clearly understood. There are various opinions as to the cause and the etiologic importance of the appearance of albuminuria.

Albuminuria is much more common in children than in adults. The urine which is secreted while the individual is in a lying posture usually presents nothing abnormal. But, as is assumed by observers and as I have also found, albuminuria does not necessarily appear in the upright position. The same individual excretes urine with a large amount of albumin one day, while it contains none the next day, and even the same day the contents and the appearance of albumin in the urine are variable. Pavy was the first to term this condition cyclic albuminuria.

As to the cause of the albuminuria, Jehle [1] believes that it is due to a venous hyperemia of the kidney brought about by a faulty position of the lumbar spine. He observed that all orthostatic albuminurics showed a lordosis in the region of the first and second lumbar vertebras. He bases his views on the examination of 300 children, and attempts to show that the lordosis is practically the only factor of importance.

Jehle's contention that the lordotic lumbar spine is the chief cause of the albuminuria has been corroborated by many investigators and denied by a few. Hooker,[2] Englander,[3] Hamburger,[4] and some others believe that there must be a second etiologic factor besides the lordosis, and they point out that vasomotor instability must play a part. Eppinger and Hess,[5] in their pharmacologic examination on the excitability of the vegetative nervous system in several kinds of diseases, observed that all the orthostatic albuminurics showed sympathicotonia.

As to the relations of the condition to other factors, many of the French observers believe that it occurs more often in children with a tuberculous family history, while others think that it may have an intimate correlation with nephritis, that is, that the condition is probably due to a relative insufficiency of the kidney.

During one year and a half, from August, 1918, to February, 1920, forty-four patients were admitted to our pediatric department who showed moderate or severe degree of orthostatic albuminuria.

* Received for publication May 26, 1921.

1. Jehle, L.: Ergebn. d. Inn. Med. u. Kinderh. **12**: 1913.
2. Hooker: Arch. Int. Med. **5**:491 (May) 1910.
3. Englander: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien, 1911.
4. Hamburger: Wien. klin. Wchnschr., 1912.
5. Eppinger, Hess: Ztschr. f. klin. Med. **67**:68, 1909.

I had an opportunity to study the following points: (1) General state of the patients; (2) excitability of the vegetable nervous system; (3) renal function with the phenolsulphonephthalein; (4) examination of blood; (5) chemical analysis of albumins in the urine and (6) provocative position of the albuminuria.

I will report here the chief results of these investigations.

I. GENERAL CONDITIONS

Fourteen patients of the forty-four had nervous diseases, namely: chorea minor, periodic vomiting, asthma and enuresis. The other thirty complained of various nervous disturbances, namely: nine of headache, eight of weariness, exhaustion and paleness, seven of palpitation of the heart, and six of turgescence and dropsy of the face. Objectively, we found enlarged tonsils in six cases; malnutrition in ten; arrhythmia and the diminution of blood-pressure in fifteen; cardiac hypertrophy in three and drop-heart in eight; the patients were all under 14 years of age. That is to say, there were no symptoms that would direct attention to the genito-urinary tract, and the condition was usually discovered in an attempt to explain the poor general condition of the patient. Sometimes symptoms of angioneurotic edema directed attention to the urine. It is worth mentioning here that the patients, in many instances, often had various neuroses, cardiac palpitation and vasomotor symptoms. The albumin content in the urine ranged from a trace to 2.8 per cent.; the acetic acid body was present without exception.

The relationship between tuberculosis and albuminuria has long been pointed out, especially by the French, who speak of a pretuberculous albuminuria. In our cases, Pirquet's tuberculin cutaneous reaction was positive in 44 per cent. This rate is not high, as most of the patients were healthy schoolboys. The Wassermann reaction, tried in eighteen anemic children, was positive in five. This also is not high, contrasted with the control patients without albuminuria. The lordosis of the lumbar spine was demonstrated in 55 per cent.; and this ratio is high, contrasted with the 32 per cent. control patients without albuminuria.

Orthostatic albuminuria may not be an independent essential disease, but, as a rule, it appears usually as a complication of some disturbance; sometimes it may be mistaken for nephritis; occasionally, it will be discovered in quite healthy individuals. But often they have nervous disturbances, are usually anemic, poorly nourished and frequently show lordosis.

Conclusion.—Orthostatic albuminurics have an asthenic constitution. About one half of them show lordosis of the lumbar region. Tuberculosis and syphilis have no etiologic bearing on the condition.

II. EXCITABILITY OF THE VEGETATIVE NERVOUS SYSTEM OF THE ORTHOSTATIC ALBUMINURICS

From their clinical investigations, Eppinger and Hess have found that there exist two groups in man, one reacting only to vagotropic drugs, and the other to sympathicotropic drugs. They named the former condition vagotonia, the latter sympathicotonia, and they included orthostatic albuminuria in sympathicotonia. Later, Beckmann and Schleyer [6] tried the same pharmacologic examinations on six adult albuminurics, but were unable to find symptoms of sympathicotonia, though they ascertained that five of the six were in the condition of so-called vagotonia.

According to recent investigators and personal experiences, the theory seems to be confirmed that there is no such strict distinction between both conditions concerning the pharmacologic reactions as Eppinger and Hess had explained. There are individuals, whose vegetative nervous system is excited either by epinephrin or by atropin. There are also cases in which neither atropin nor pilocarpin show their paralyzing or stimulating effect on the parasympathetic nervous system in the same degree. In spite of these irrationalities, the test by Eppinger and Hess may be an instructive and an interesting method to ascertain the general conditions as to the irritability of the vegetative nervous system in various disturbances.

I have proved the test on seventeen albuminurics; all being children under 15, with exception of one adult. I usually repeated the test twice on the same person (Table 1).

TABLE 1.—DOSAGE OF THE MEDICINE SUBCUTANEOUSLY EMPLOYED

Weight of Body	Dose of Medicine *
Under 10 kilo	0.1 c.c.
10–20 kilo	0.2 c.c.
20–30 kilo	0.3 c.c.
30–40 kilo	0.4 c.c.
40–50 kilo	0.5 c.c.

* Epinephrin and atropin, 1 o/oo solution; Pilocarin, 1 o/o solution.

Technic and Criticism of Results.—The frequency of pulse reaction, and the size of the pupils, the blood pressure, previously repeatedly examined, were noted and the average number taken; then the drug was injected subcutaneously. After the injection, the frequency of the pulse rate and the blood pressure must be taken every ten or fifteen minutes. Moreover, the condition of the skin, as to whether it becomes warmer, moister, shows sweating or redness, must be noted. The urine is tested for albumin and sugar before and after the examination. The whole experiment requires three days, one day for each of the

6. Beckmann, Schleyer: Münch. med. Wchnschr. No. 2, 1918.

three medicines employed. We called the results positive according to the following rules:

1. EXPERIMENT WITH EPINEPHRIN: Cases, in which either the pulse frequency increases more than twenty per minute, or the blood pressure increases more than 20 mm. Hg., or if glycosuria is present, are in the condition of sympathicotonia.

2. EXPERIMENT WITH PILOCARPIN: Cases in which sweating, salivation, redness of the face and hotness of the whole body were observed, or nausea, or the blood pressure increased more than 20 mm. Hg., are classed as vagotonia, namely parasympathicotonia.

3. EXPERIMENT WITH ATROPIN: Cases, in which thirst, or redness of the face and hotness of the body appeared, or the pulse frequency increased more than twenty in a minute, are classed as vagotonia namely, parasympathicotonia.

It is important to note that the influence of pilocarpin and atropin on the pulse ratio and the blood pressure are not constant and not so excellent in children as they are in adults. Some illustrative cases are given here:

REPORT OF CASES

CASE 1.—K. S., healthy male, aged 15 years and 4 months. This boy I found occasionally at the swimming-place. I was engaged at that time in the study of albuminuria among swimmers, and I discovered an abundant quantity of albumin in this boy's urine. Observation during the course of about two years showed that this was an indubitable case of orthostatic albuminuria.

Physical Examination.—Drop heart; lordosis of the lumbar spine; tuberculin reaction positive; albumin content in urine from trace to 3 o/oo.

Pharmacologic Examination of Vegetative-Nervous System.—

September 8: Weight 57.8 kg.; 1 o/o pilocarpin sulphate solution, 0.6 c.c. injected

	Pulse Ratio	Blood Pressure	Remarks
Before infection	72	106 mm.	
After injection 5′	78	104 mm.	
After injection 10′	82	103 mm.	Salivation
After injection 15′	84	104 mm.	Sweating, feeling of hotness, redness of the face
After injection 20′	86	110 mm.	All increased. Stranguary
After injection 30′	86	121 mm.	Sweating and salivation increased
After injection 40′	82	117 mm.	All diminished

October 8: 1 o/oo atropin sulphate solution, 0.6 c.c. injected

	Pulse Ratio	Blood Pressure	Remarks
Before injection	64	115 mm.	
After injection 5′	58	107 mm.	
After injection 10′	54	103 mm.	
After injection 15′	66	102 mm.	A slight thirst
After injection 20′	66	101 mm.	
After injection 30′	66	102 mm.	Thirst increased
After injection 40′	66	99 mm.	Redness of the face
After injection 60′	64	99 mm.	Thirst yet present

November 8: 1 o/oo epinephrin solution, 0.6 c.c. injected

	Pulse Ratio	Blood Pressure	Glycosuria	Remarks
Before injection	68	105 mm.	(—)	
After injection 5′	68	105 mm.	....	Hotness of body
After injection 10′	74	102 mm.	....	Fatigue, tremor of finger
After injection 15′	78	120 mm.	....	Palpitation of the heart, paleness of the face
After injection 20′	78	125 mm.	....	Thirst present, palpitation diminished
After injection 30′	86	135 mm.		
After injection 40′	80	122 mm.		
After injection 50′	74	114 mm.	(—)	Thirst and hotness diminished

In this case the vegetative nervous system was sensitive toward all the reagents, especially to atropin and pilocarpin (Table 1).

CASE 2.—H. N., male, aged 10 years and 6 months, admitted as a case of orthostatic albuminuria March 21, 1919, having suffered from paleness and palpitation for two years, and onset of headache with fever occurring every month for one year and lasting a few days.

Physical Examination.—Anemic; musculature flabby; tuberculin reaction negative; Wassermann reaction doubtfully positive; no drop heart; no lordosis. Albumin content ranging from a trace to 0.15 o/oo

Pharmacologic examination of the vegetative nervous system was repeated three times, the result always being the same; it was negative for epinephrin, positive for atropin and pilocarpin (Table 2). Moreover, it was found that similar symptoms appeared as those given in the tables above, after the administration of atropin.

March 26: 1 o/oo epinephrin, 0.25 c.c. Weight: 25.2 kilo

	Pulse Ratio	Blood Pressure	Glycosuria
Before injection	96-102	90 mm.	(—)
After injection 5′	96	90 mm.	
After injection 10′	102	90 mm.	
After injection 15′	96	87 mm.	
After injection 20′	96	87 mm.	
After injection 30′	102	87 mm.	
After injection 40′	96	90 mm.	(—)

March 27: 1 o/o pilocarpin, 0.25 c.c.

	Pulse Ratio	Blood Pressure	Remarks
Before injection	96	88 mm.	
After injection 5′	96	80 mm.	Salivation, hotness
After injection 10′	96	85 mm.	
After injection 15′	100	86 mm.	Increased
After injection 20′	96	84 mm.	
After injection 30′	96	83 mm.	
After injection 40′	100	86 mm.	Feeling of hotness vanished, no sweating at any time

March 29: 1 o/oo atropin, 0.25 c.c.

	Pulse Ratio	Blood Pressure	Remarks
Before injection	98	83 mm.	
After injection 5′	92	83 mm.	Headache, thirst
After injection 10′	88	82 mm.	
After injection 15′	84	82 mm.	
After injection 20′	82	83 mm.	All increased
After injection 30′	82	85 mm.	
After injection 40′	90	90 mm.	
After injection 50′	90	88 mm.	
After injection 60′	90	90 mm.	Thirst vanished
After 1 hour 10′	90	87 mm.	
After 1 hour 20′	90	88 mm.	Headache still present

CASE 3.—M. I., a clerk, aged 33 years.

History.—Empyema of antrum Highmorii operated four years ago; since then he became very nervous. Palpitation of heart, headache and fever appeared frequently after a trivial psychic condition. He was considered to be a neurasthenic by a physician. A month ago, albuminuria was found occasionally by another physician, and the condition was diagnosed as nephritis by him. I found him to be an orthostatic albuminuric.

Physical Examination.—Constitution normal; very nervous; anemic; irregular pulse; slight lordotic in lumbar spine, distinct drop heart; tuberculin reaction negative. Albumin content in urine varies from trace to 4 o/oo; no abnormal casts and no cylindroids.

Pharmacologic examination of the vegetative nervous system.—The experiment was twice repeated during the course of a year and the vegetative nervous system was sensitive to all tests, especially to atropin. Paresis of the accommodation muscle and fatigue of the body continued for three days after the atropin injection; sleeping was disturbed on account of sweating after

the pilocarpin injection; suprarenal glycosuria continued for twenty-four hours. The patient felt well after the administration of epinephrin and pilocarpin, and indisposed after atropin injection.

November 20: 1 o/oo epinephrin, 0.6 c.c. Weight: 50.4 kilo

	Pulse Ratio	Blood Pressure	Remarks
Before injection	82	125 mm.	No sugar in urine
After injection 5′	82	125 mm.	
After injection 10′	86	127 mm.	Palpitation
After injection 15′	96	130 mm.	Palpitation
After injection 20′	100	137 mm.	Paleness of face
After injection 30′	102	140 mm.	Paleness of face
After injection 40′	100	138 mm.	Palpitation and paleness slightly diminished
After injection 50′	102	140 mm.	
After 1 hour 20′	102	130 mm.	Sugar in urine (++)

November 21: 1 o/o pilocarpin, 0.6 c.c.

	Pulse Ratio	Blood Pressure	Remarks
Before injection	76	128 mm.	Salivation, hotness
After injection 5′	86	120 mm.	Sweat
After injection 10′	90	120 mm.	Hotness vanished, chilly
After injection 15′	86	130 mm.	Chill increased; salivation diminished
After injection 20′	86	130 mm.	
After injection 30′	80	120 mm.	
After injection 40′	78	120 mm.	
After injection 50′	88	115 mm.	Chill increased; salivation still exists

November 22: 1 o/oo atropin, 0.6 c.c.

	Pulse Ratio	Blood Pressure	Remarks
Before injection	80	128 mm.	
After injection 5′	76	120 mm.	Palpitation begins
After injection 10′	136	115 mm.	
After injection 15′	136	110 mm.	Mydriasis, weakness of vision
After injection 20′	134	110 mm.	Sensation of exhaustion
After injection 30′	132	110 mm.	Exhaustion increases, thirst
After injection 40′	132	115 mm.	Thirst increases, palpitation diminishes
After injection 50′	142	115 mm.	
After injection 60′	138	113 mm.	Giddiness
After 1 hour 30′	146	128 mm.	Thirst, mydriasis and paresis of pupils and exhaustion still present. The patient cannot sit up

The results are summarized in Table 2; abbreviated to describe the excitabilities of the vegetative nervous system in each case.

As Table 2 shows, twelve individuals (70 o/o) were in the condition of an abdominal tonus of the parasympathetic nervous system, three (17.6 o/o) were of an abdominal tonus of both the parasympathetic and sympathetic nervous systems, and two persons were normal. In no instance were we able to find the condition of only sympathicotonia.

Conclusion.—In opposition to the experiment by Eppinger and Hess we came to the conclusion that a large majority of the orthostatic albuminurics are in the state of vagotonia.

III. RENAL FUNCTION WITH THE PHENOLSULPHONEPHTHALEIN TEST

So far as I know, Hempelmann[7] was the first who tried the phenolsulphonephthalein test in orthostatic albuminuria. He selected seven marked cases of the so-called lordotic type and found that all but one came within the limits of the normal, as regards phthalein output when in normal position. The other one was slightly below the average, but hardly enough to call the phthalein output abnormal. The seven cases averaged 69 per cent. output in two hours, and 56.6 per cent. in one hour.

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7. Hempelmann: Am. J. Dis. Child. **10**:70 (July) 1915.

I tried the test twenty-eight times on twenty patients with marked orthotic albuminuria. In the test, 0.6 gm. phenolsulphonephthalein, contained in 1 c.c. of solution, were injected intravenously, as advised by Rowntree and Geraghty. The urine was collected separately at different times after injection and the amount of phenolsulphonephthalein present in each specimen was estimated by means of a Du Boscq colorimeter. The children were allowed to take their voluntary positions after the injection. Table 3 summarizes the results.

TABLE 2.—EXCITABILITY OF THE VEGETATIVE NERVOUS SYSTEM

Case No.	Date	Age in Yrs.	Sex	Diagnosis and Clinical Findings	Pharmacologic Examination		
					Atropin	Pilocarpin	Epinephrin
1a	Jan., 1918	15	♂	Drop heart, lordosis. Pirquet: minimum positive	+	+	—
1b	Aug., 1919	..	..		+	++	+
2a	Feb., 1919	10	♂	Anemia, flabby muscle. Pirquet: negative	+	+	—
2b	Mar., 1919	..	..		++	+	—
3a	Nov., 1919	33	♂	Anemia, slight lordotic, distinct drop heart. Pirquet: negative	+++	+++	++
3b	May, 1920	..	..		+++	+++	++
4a	Jan., 1919	13	♂	Lordosis, dropsy of face, cardiac hypertrophy. Pirquet: negative.	—	+	—
4b	Jan., 1919	..	..		—	++	—
5	Jan., 1919	13	♂	Chorea minor. Lordosis. Pirquet: negative	—	+	—
6	Feb., 1919	12	♂	Lordosis, drop heart, flabby muscle. Pirquet: negative	—	+	—
7a	Mar., 1919	8	♂	Periodic vomiting. Paleness and dropsy of face. Pirquet: negative	—	—	—
7b	June, 1919	..	..		—	—	—
8	Mar., 1919	13	♂	Edema, lordosis. Pirquet: negative	—	+	—
9a	Apr., 1919	13	♀	Asthma. Wassermann's and Pirquet's reaction positive	—	++	—
9b	May, 1919	..	..		—	++	—
10	Apr., 1919	10	♀	Periodic vomiting. No lordosis; Pirquet: negative	—	—	—
11	June, 1919	10	♂	Nervous, flabby muscle, atrophic heart; Pirquet positive	++	+	—
12	Aug., 1919	12	♂	Empyema of antrum Highmorii. flabby muscle, lordosis, drop heart. Pirquet, negative	++	++	—
13a	July, 1919	7	♂	Enlargement of thymus. Atrophic heart, lordosis. Pirquet positive	++	—	—
13b	Nov., 1919	..	..		++	±	—
14	Apr., 1919	12	♂	Paleness and dropsy of face, flabby muscle, lordosis, cardiac hypertrophy. Pirquet negative	++	—	—
15	July, 1919	12	♂	Asthma, enlarged tonsils, flabby muscle, lordosis. Pirquet positive	+	—	—
16	Aug., 1919	13	♂	Paleness, flabby muscle, irregular pulse. Pirquet positive	++	+	—
17	Aug., 1919	11	♂	Nervous, atrophic, flabby muscle, irregular pulse. Pirquet negative	+++	++	+

As Table 3 shows, renal function measured by the phenolsulphonephthalein test, except in one case (Case 19), was within normal limits. Although the percentage of the excretion of phthalein is usually constant in the same individual, there may be exceptions, as in Case 15. We also know that there is no definite relation between the amount of phthalein output and the degree of lordosis of the lumbar spine.

Conclusion.—Renal function of the orthostatic albuminurics, as measured by the phenolsulphonephthalein output, is generally normal.

IV. EXAMINATION OF BLOOD

In regard to the blood features in cases of this condition, so far as I know, only Langstein [8] records that there is no particular change in the blood count. Since children in this condition are almost always anemic, this study was undertaken. I have made blood counts forty-five times in twenty-two undoubted cases; The results are shown in Table 4.

TABLE 3.—PHENOLSULPHONEPHTHALEIN EXCRETION IN ORTHOSTATIC ALBUMINURIA

Case No.	Age in Yrs.	Date	After 30 Min.	After 1 Hr.	After 2 Hrs.	Total	Average, o/o	Remarks
1	13	5/16/19	55	7,5	0,5	63,0	66,8	Asthma, distinct lordosis
		5/16/19	60	10	0,7	70,7		
2	12	5/10/19*	23	20	15	58,0	57,5	Lordosis, middle degree
		8/ 8/19	32,5	15	10	57,5		
3	13	8/19/19	60	10	5,0	75,0	75,0	Slight lordosis
4	12	8/ 7/19	50	12,5	5,0	67,5	65,0	Slight lordosis
		8/ 8/19	45	10	7,5	62,5		
5	10	6/14/19	50	15	10	75,0	75,0	No lordosis
6	12	8/19/19	55	15	5,0	75,0	75,0	Lordosis slight; asthma
7	11	11/20/19	35	17	10	62,0	62,0	No lordosis
8	12	7/25/19	35	10	5,0	50,0	50,0	Lordosis distinct
9	7	7/25/19	55	15	5,0	75,0	75,0	Lordosis slight
10	13	5/30/19	40	20	20	80,0	80,0	No lordosis
11	8	6/14/19	40	20	15	75,0	75,0	No lordosis, periodic vomiting
12	12	11/ 4/19	60	15	5,0	80,0	80,0	Lordosis distinct
13	13	10/ 1/19	40	25	15	80,0	80,0	No lordosis, chorea
14	12	9/24/18	35	25	15	75,0	80,0	No lordosis
		9/ 6/19	65	15	5,0	85,0		
15	33	9/19/19	22,5	12,5	8,0	43,0		
		11/21/19	65.0	10	5,0	80,0	63,2	Lordosis slight, neurasthenia
		11/24/19	57,5	10	5,5	73,0		
		5/11/20	40,0	10	7,0	57,0		
16	16	8/14/18*	..	55	25	80,0	80,0	
		8/14/19	55	20	5,0	80,0		
17	13	2/19/19	45	7,5	7,5	60,0	60,0	No lordosis
18	11	2/25/19	55	2,5	2,5	60,0	60,0	No lordosis
19	12	3/ 8/19	20	7,5	15	42,5	42,5	No lordosis
20	9	3/ 8/19	50	7,5	2,5	60,0	60,0	Lordosis distinct

* Phthalein injected into the muscles.

As to the ratio of leukocytes, in eight cases, a slight increase was observed. In spite of an anemic appearance and dropsy of the face, we could confirm that both the hemoglobin and the number of red corpuscles in the blood were in normal ratio. If we can assume that the number of eosinophilic cells in the blood averages less than 5 per cent. normally, there were thirteen cases in which an increase of the cells was recognized. Excluding two cases of asthma, one case of thymus enlargement, and one of ancylostomo anemia, we found eosinophilia in the remaining nine cases (41 o/o).

These three blood changes in orthostatic albuminuria,—pseudo-anemia, leukocytosis and eosinophilia,—especially the presence of an unusual number of eosinophilic cells in the blood, may not be of an accidental nature, but a phenomenon more closely related to the condition of vagotonia, as already stated.

8. Langstein, L.: Handbuch d. Kinderh., by Pfaundler and Schlossmann, Ed. 2; **4:**

TABLE 4.—Blood Counts in Cases of Orthostatic Albuminuria

Case No.	Age, Years	Date	Remarks	Hemoglobin, o/o	Erythrocytes	Leukocytes	Polynuclear Neutrophils, o/o	Lymphocytes, o/o	Mononuclear Leukocytes, o/o	Transitional Forms, o/o	Eosinophils, o/o	Basophils, o/o
1	16	Aug. 9, 1918	No anemia	85	4,840,000	12,000	58.5	15 0	3.5	4.5	18.0	0.5
		Aug. 14	No anemia	85	5,008,000	5,200	51.0	20.0	3.5	4.0	21.0	0.5
		Aug. 30, 1919	No anemia	90	4,480,000	8,100	60.5	21.0	2.5	3.0	12.5	0.5
2	10	March 24	Anemia, dropsy of face	72	5,006,000	15,200	60.0	33.5	1.0	4.0	1.0	0.5
		March 29		68	4,956,000	12,400	62.0	27.6	2.0	5.0	3.4	—
3	12	Nov. 5	Anemia, dropsy of face	80	5,048,000	8,200	53.0	32.0	3.0	4.0	8.0	—
4	12	March 4	Anemia, dropsy of face	70	4,000,000	12,600	64.0	24.0	4.6	4 6	2.6	0.2
		Nov. 4	Anemia, dropsy of face	75	4,800,000	9,600	60.0	28.0	4.0	5.0	3.0	—
5	8	March 3	Anemia, prurigo	80	4,720,000	13,000	57.1	28.5	3.1	9.3	2.0	—
		March 6	Anemia, prurigo	80	4,640,000	12,600	58.0	28.5	2.0	5.0	6.0	0.5
		March 25	Anemia, prurigo	80	4,888,000	9,000	59.0	30.0	2.0	5.0	4.0	—
		June 19	No eruptions	75	3,736,000	7,800	42.0	48.5	2.5	3.0	4.0	
6	13	March 28	Anemia, dropsy of face	70	4,900,000	6,000	58.4	26.8	2.4	5.6	6.8	—
		April 2	Anemia, dropsy of face	70	4,248,000	7,200	59.2	32.1	4.6	2.6	0.5	—
7	7	July 23	Enlargement of thymus before x-ray application	60	4,800,000	11,400	57.5	31.0	1.5	2.5	7.5	—
		July 31	X-ray treatment 2 times	80	4,600,000	8 800	62.5	26.5	2.0	2.0	7.0	—
		Aug. 20	X-ray treatment 4 times	85	4,304,000	138,00	53.4	30.0	1.4	4.0	10.6	—
		Sept. 5	X-ray treatment 7 times	85	5,000,000	7,800	61.0	26.5	1.0	2.0	9.5	—
		Nov. 28	70th day from interruption	90	3,956,000	2,240	69.5	20.7	1.3	2.2	6.3	—
		Nov. 29	71st day from interruption	90	3,840,000	2,840	70.0	19.4	2.0	2.6	6.0	—
8	12	July 30	Anemia, dropsy of face	65	3,876,000	9,200	50.5	36.5	2.0	3.0	8.0	—
9	11	Nov. 20	Anemia	100	5,216,000	6,250	40.0	54.0	1.0	2.0	3.0	—
10	12	Aug. 20	No anemia, asthma	86	5,144,000	7,800	51.0	23.5	3.0	4.0	18.5	—
11	10	June 23	Anemia, nervous	72	3,648,000	8,600	44.6	43.5	5.3	6.0	10.0	0.6
12	8	March 25	Anemia	80	4,348,000	7,800	50.3	32.0	5.0	7.7	4.0	1.0
		March 29	Anemia	80	3,972,000	13,400	62.0	26.5	1.5	8.0	2.0	—
13	12	Aug. 3	No anemia	80	3,552,000	6,400	58.5	32.0	2.5	4.0	3.0	—
		Aug. 9	No anemia	85	4,200,000	6,200	58.1	30.9	3.6	4.5	2.7	0.2
14	13	Aug. 14	Anemia	86	4,156,000	7,800	54.5	36.5	2.5	2.5	4.0	—
		Aug. 16	Anemia	85	4,700,000	7,500	59.0	31.0	2.0	3.0	5.0	—
15	10	April 15	Anemia, dropsy of face	80	3,924,000	7,400	57.5	32.5	4.0	2.5	3.0	0.5
		April 18	Anemia, dropsy of face	80	4,484,000	7,800	57.0	35.0	4.0	2.5	1.5	—
		April 30	Anemia, dropsy of face	80	4,045,000	7,200	48.1	45.6	1.8	2.5	1.8	0.2
16	12	April 26	Anemia, dropsy of face	90	4,200,000	8,200	50.6	24.0	1.5	3.3	20.0	0.6
		Aug. 10	Anemia, dropsy of face	90	3,940,000	8,600	41.0	28.0	1.0	3.0	27.0	—
17	13	April 17	Anemia, asthma	80	4,568,000	11,200	55.5	18.5	2.0	3.0	21.0	—
		April 22	Anemia, asthma	80	4,216,000	8,600	49.3	21.0	1.6	2.2	25.3	0.6
		May 10	Anemia, asthma	100	4,656,000	9,800	37.6	17.6	5.3	4.3	35.2	—
		May 17	Anemia, asthma	100	4,680,000	6,000	45.0	25.0	2.0	3.0	25.0	—
18	33	Nov. 21	Anemia, neurasthenia	100	5,664,000	5,400	63.0	24.0	3.0	5.0	5.0	—
		Nov. 22	Anemia, neurasthenia	100	5,444,000	5,600	60.0	28.0	2.0	4.0	6.0	—
19	13	Feb. 19	Edema of face, anemia	95	4,135,000	5,400	48.5	40.0	3.0	3.0	5.5	—
20	11	Feb. 28	Dropsy of face	100	5,712,000	12,200	44.5	38.0	2.0	4.0	11.5	—
21	12	March 8	Anchylostoma-anemia	100	.....	.....	57.5	33.0	1.o	3.0	5.0	—
22	9	March 11	No anemia, enuresis	98	5,260,000	7,600	60.0	23.5	1.0	3.0	12.0	0.5

Conclusion.—The blood features in orthostatic albuminuria are characterized by pseudoanemia, eosinophilia and occasionally leukocytosis.

V. CHEMICAL ANALYSIS OF ALBUMINS IN THE URINE

Langstein [9] believed that the substance in the urine precipitated on the addition of cold acetic acid, was probably euglobulin. According to Pollitzer,[10] the precipitate is caused by a combination of serum albumin and chondroitin-sulphuric acid. In my experience, the occurrence of this so-called acetic acid body in the urine, is not limited to this form of albuminuria, for it appears not only in nephritic urines but also in all exudates and transudates.

I have analyzed the urine in three cases with regard to the acetic acid body, globulin and albumin and compared the results with those of a purulent cerebrospinal fluid of an epidemic meningitis.

Method: Set aside the precipitated salts in alkaline reaction, add a small amount of ammonia solution to the urine, filter the sediments then add acetic acid solution to make the reaction of the urine just neutral. To estimate the nitrogen value of the acetic acid body, from 100 to 200 c.c. are measured exactly, then acetic acid is added in the ratio of 0.2 per cent.; after twenty-four hours it is filtered and the precipitate repeatedly washed with 0.2 per cent. solution of acetic acid, and then the nitrogen content is measured with Kjeldahl's. Of the filtrate, globulin and albumin are measured separately after Hofmeister's method.[11] The results are as follows:

Case 1a, female, aged 13 years. Urines collected from April 30 to May 6:

	o/oo		
Nitrogen of total proteids	0,118		
Nitrogen of acetic acid-body	0,027	=	25,2 o/o
Nitrogen of globulin	0,028	=	26,1 o/o
Nitrogen of albumin	0,052	=	48,6 o/o

The albumin quotient = 1,85 : 1

Case 1b, the same patient. Urines collected from May 9 to May 12

	o/oo		
Nitrogen of total proteids	0,144		
Nitrogen of acetic acid-body	0,016	=	16,6 o/o
Nitrogen of globulin	0,038	=	39,5 o/o
Nitrogen of albumin	0,042	=	43,7 o/o

The albumin quotient = 1,10 : 1

Case 2, male, aged 10 years

	o/oo		
Nitrogen of total proteids	0,267		
Nitrogen of acetic acid-body	0,032	=	12,1 o/o
Nitrogen of globulin	0,100	=	38,0 o/o
Nitrogen of albumin	0,131	=	49,8 o/o

The albumin quotient = 1,31 : 1

Case 3, male, aged 15 years

	o/oo		
Nitrogen of total proteids	0,258		
Nitrogen of acetic acid-body	0,042	=	15,4 o/o
Nitrogen of globulin	0,084	=	30,8 o/o
Nitrogen of albumin	0,146	=	53,6 o/o

The albumin quotient = 1,74 : 1

9. Langstein, L.: Die Albuminurie älterer Kinder, Monograph, Leipzig, 1907.
10. Pollitzer: Deutsch. med. Wchnschr. March, 1912.
11. Hofmeister u. Pohl: Arch. f. exper. Pathol. u. Pharmakol. **20:** 1886.

Case 4, cerebrospinal fluid of a case of epidemic meningitis. Patient, male, aged 8 years. Collected four puncture fluids

	o/oo		
Nitrogen of total proteids	0,364		
Nitrogen of acetic acid-body	0,045	=	15,8 o/o
Nitrogen of globulin	0,097	=	34,1 o/o
Nitrogen of albumin	0,142	=	50,0 o/o

The albumin quotient = 1,19 : 1

Conclusion.—The quantity of the acetic acid body in the urine of the orthostatic albuminurics varies both in absoluteness and in relativeness in the same individual. The albumin quotient of the proteids in the urine is exactly equal to the serum and the cerebrospinal fluid.

VI. PROVOCATIVE POSITION OF THE ALBUMINURIA

Jehle's contention that the lordotic lumbar spine is the chief cause of the albuminuria has been corroborated by some investigators and denied by a few. They think that there must be a second etiologic factor besides the lordosis. Bruch [12] took normal nonlordotic children and put them in lordotic position by letting them kneel. Of the forty-four children examined, 18 per cent. showed albumin. He concluded that "albuminuria provocativa orthostatica cannot in any manner be used to differentiate various types of children nor to distinguish various degree of renal sufficiency. B. Vas [13] reports observation on 150 girls ranging in age from 9 to 14 years. Of these, sixty-two had albuminuria, and twenty-six of these showed the orthostatic variety. Examining these twenty-six, he found albumin associated with lordosis in fifteen cases; albumin without lordosis in eleven cases. He also found nine cases with lordosis, but without albuminuria. He concluded that orthostatic albuminuria occurs about as often with lordosis as without it.

In forty cases of orthostatic albuminuria, I tried four different kinds of position to see in what posture albuminuria appears constantly.

Position 1: Forced lordosis in dorsal position, by causing an artificial lordosis of the spine by means of inserting a wooden pillow under the loin for ten minutes.

Position 2: Standing lordotic position, inclining the upper half of the body to the right or to the left for ten minutes. If the appearance of albuminuria is due to a venous hyperemia of the kidney, it must be produced most distinctly by a position of artificial lordosis with the right sided inclination of the upper part of the body.

Position 3: Forced upright position, letting the individual hold up the arms to the level of the shoulders with a rod, for ten minutes (Fig. 1).

Position 4: A kneeling posture for ten minutes (Fig. 2).

The former two positions cannot be recommended for all cases, because they cause pain, often result in dangerous sequels and some-

12. Bruck: Münch. med. Wchnschr. No. 44, 1908.
13. Vas, B.: Deutsch. med. Wchnschr. No. 34, 1909.

times give a negative result. The two last positions, one making the patient hold a rod with two hands and lifting it up to the level of the shoulder, and the other bidding the patient kneel down, are the most reliable and the safest methods to produce albuminuria; it can be applied in all cases without trouble or danger (Tables 5 and 6).

I examined these two positions on ninety-six sick children; the forced upright position on forty-seven and the kneeling position on forty-nine. They all had organic diseases, some were markedly neuro-

Left.—Forced upright position (albuminuria provocative position).
Right.—Kneeling position (albuminuria provocative position).

pathic, some had peritonitis and pleuritis; thirty-one had some fever; five had nephritis and thirty-two showed lordosis. Of these ninety-six children, only 3 children, one on the forced upright and two on the kneeling position, showed slight albumin.

I also examined for albuminuria on 148 healthy school boys, ranging in age from 10 to 14 years. Of these, twenty-two (14.8 per cent.) had albuminuria; seven (30 per cent.) showed lordosis. I tried the forced upright position on these twenty-two albuminurics and found that twenty (90 per cent.) showed a great excretion of albumin.

From these observations I can state, that these two positions to provocate albuminuria can be used to differentiate the nature of albuminuria, and as a diagnostic method to detect orthostatic albuminurics if no albumin is found in urine during consultation. It is important to note that the forced posture should not exceed ten minutes.

TABLE 5.—Case 1. Healthy Lordotic Boy with Orthostatic Albuminuria. Fifteen Years Old

Date	Position and Remarks	Urine Findings				
		Reaction	Sp. Weight	Acetic-Body	Proteids	Cylindroids
Aug. 13, 1918	Comes from 3 miles distance on foot...	Alkaline	1.007	(+)	Trace	(—)
Aug. 14, 1918	Comes by tram.....	Alkaline	1.015	(+)	Trace	(—)
Aug. 9, 1919	Ran 5 miles early in the morning. Urine at 9:30 a.m.	Alkaline	1.016	(+++)	1.0 o/oo	(—)
	Urine at 1 p.m.	Alkaline	1.018	(+)	0,1 o/oo	
Aug. 10, 1919	Swimming afternoon, tired. Urine at 7 p.m.	Acid	1.022	(—)	(—)	(—)
Aug. 21, 1919	2 p.m.	Acid	1.020	(—)	(—)	(—)
	Kneeling position for 10 min., urine after 1 hour.....	Neutral	1.018	(+++)	1,0 o/oo	(—)
Aug. 30, 1919	11:30 a.m.	Neutral	1.007	(—)	(—)	(—)
	Forced upright position for 10 min., urine after 20 min.	Acid	1.022	(+++)	1,5 o/oo	Scanty cylindroids
	Kneeling position for 10 min. successively, urine after 20 minutes.....	Acid	1.008	(++++)	2,5 o/oo	Scanty granulated cylindroids and erythrocytes

TABLE 6.—Case 2. Non-Lordotic Orthostatic Boy with Anemia and Dropsy Appearance. Thirteen Years Old

Date	Position and Remarks	Urine Findings				
		Reaction	Sp. Weight	Acetic-Body	Proteids	Cylindroids
Sept. 21, 1918	1:30 a.m.	Acid	1.021	(++)	(—)	(—)
Oct. 7, 1918	At noon time.....	Acid	1.008	(—)	(—)	(—)
	Standing at will for 10 minutes.....	Acid	1.008	(—)	(—)	(—)
	Forced lordosis in dorsal position for 10 minutes.....	Acid	.....	(—)	(—)	(—)
	After walking for 10 minutes.....	Acid	1.007	(—)	(—)	(—)
	Forced upright position for 10 minutes	Acid	1.007	(++)	0,1 o/oo	(—)
Sept. 5, 1919	2 p.m.	Acid	1.020	(+)	0,17 o/oo	(—)
	After kneeling position for 10 minutes	Acid	1.020	(+++)	3,0 o/oo	(—)
	After free position for 40 minutes successively.....	Acid	1.022	(+)	0,03 o/oo	(—)
	After a lying position for 30 minutes successively.....	Acid	1.018	(+)	(—)	(—)

If this condition is observed, these two postures may be used for diagnosis.

Conclusion.—The two methods: The first, or position where the patient holds a rod with two hands and lifts it up to the level of the

shoulder; and the second, the kneeling position, are both safe and reliable means to provocate albuminuria. The time is limited to ten minutes or less. Cases with no albumin in the pre-urine and albumin in the after-urine, may be classed as orthostatic albuminuria.

SUMMARY

1. Orthostatic albuminurics have an asthenic constitution. About half of them show lordosis.

2. Tuberculosis and syphilis have no bearing on the condition.

3. A large majority of the orthostatic albuminurics are in the state of vagotonia.

4. Renal function of the orthostatic albuminurics, as measured by the phenolsulphonephthalein test, is generally normal.

5. Despite anemia, a vast majority of them have a normal hemoglobin content in the blood. Further, there is often found an eosinophilia and occasionally a leukocytosis.

6. The amount of the acetic acid body in the urine varies either absolutely or relatively even in the same individual.

7. The albumin quotient of the proteids in the urine is equal to that of the serum and of the cerebrospinal fluid.

8. Two methods, one to have the individual hold a rod with the hands and lift it up to the level of the shoulder for ten minutes, and the other to have him kneel down for ten minutes, are most reliable to provoke albuminuria. The time is limited to ten minutes. These positions may be employed for diagnosis.

9. The direct cause of albuminuria may be lordosis of the lumbar spine. Albuminuria, however, does not occur with merely a lordosis; and vasomotor instability is also thought to be a factor.

A STUDY OF THE INCIDENCE OF HEREDITARY SYPHILIS *

P. C. JEANS M.D. AND J. V. COOKE, M.D.
ST. LOUIS

The incidence of syphilis in various communities has been the subject of some study and much speculation. Groups of individuals have been examined by different observers, and the incidence of the disease in these groups has been assumed to indicate its prevalence in the community. It is evident, however, to all who examine such group studies that the groups observed are not truly representative of the entire community and that any estimates based on them are consequently open to criticism. As recently as December, 1920, the All-America Conference on Venereal Disease concluded that "no reliable statistics are available at the present time"; this applies equally to the hereditary as well as the acquired form of the disease. Several estimates have been made of the incidence of hereditary syphilis based on group studies,[1] but none is based on observations that render it applicable to the general population. To illustrate some of the fallacies of these estimates, it is only necessary to call attention to the errors of employing selected groups of individuals. All studies not based primarily on Wassermann reactions do not include the latent cases which form a considerable percentage and in infants this test is not always reliable until after the second month. Studies on hospital and dispensary patients give the incidence only in the poorer class and more particularly in the sick of this class. Such studies also must be based on routine Wassermann tests made on every admission. All estimates which depend on the examination of older children do not take into account stillborn infants and those dead in early infancy, although it is well recognized that many of these are due to hereditary syphilis. Also, few attempts have been made to secure figures applicable to the well-to-do classes if one may so designate those whose income is above that of dispensary patients. A true estimate of the incidence of hereditary syphilis, therefore, must be based on observations which include all children born in a group of unselected families of all classes.

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*From the Department of Pediatrics, Washington University Sschool of Medicine and the St. Louis Children's Hospital.

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1. Jeans, P. C.: A Review of the Literature of Syphilis in Infancy and Childhood, Am. J. Dis. Child. **20**:55 (July) 1920.

The study presented in this paper represents an attempt to make an estimate of the incidence of syphilis based on a representative group of unselected individuals. Such a group was obtained by taking a series of all pregnant women delivered during a period of eight months from several constant sources. These included four hospitals caring for those able to pay the fees charged private patients, and the charity cases cared for in two hospitals and two out-patient obstetrical clinics. In all 2,030 families are represented, with approximately one-fifth of the children born in St. Louis during the period studied. These were almost equally divided between charity and private patients. Since syphilis is not a factor in sterility,[2] no selection occurs in a group of this kind.

The basis of the study was the histologic examination of all placentas together with a Wassermann reaction on the fetal blood collected from the umbilical cord at birth. Before using the results of these examinations as a means of estimation of the incidence of syphilis, it was necessary to determine their value as an indication of the presence or absence of the disease in the infant, or, in other words, to what extent an agreement occurred between the placental histology and the fetal blood Wassermann reaction on the one hand and the living infant on the other. For this purpose Wassermann reactions were obtained on as many infants as possible two months or more after birth together with a similar test on the mothers at that time. These additional examinations were possible only among the poorer class who could be persuaded to return for "post natal" observation and of this group we were able to reexamine in this way more than 35 per cent.

Before giving the results of the study, it is necessary to mention briefly the criteria used in determining the presence of syphilitic changes in the placenta, and the method of performing the Wassermann reaction.

The morphologic alterations usually considered characteristic of syphilis in the placenta are those in the chorionic villi and consist of a thickening or "clubbing" by increase in connective tissue, with a marked decrease in vascularity. While other changes such as endarteritis and perivascular infiltration by lymphocytes are also sometimes encountered, these latter are not characteristic. It is obvious that unless the distinguishing histologic lesion is a diffuse one, it will be recognized only by examining a number of portions of the placenta. While in certain cases it can be shown that some parts of a placenta are normal microscopically and other areas give a typical picture of placental syphilis, in a study of this kind multiple sections could not be examined in each instance. Only those placentas in which the changes were

2. Jeans, P. C.: Syphilis and Its Relation to Infant Mortality, Am. J. Syphilis, **3**:114 (Jan.) 1919.

apparently diffuse, therefore, would have been considered positive by our method of examination. As the study progressed, certain placentas were encountered in which small portions of the section or certain villi had some of the characteristic "clubbing" or some decrease in vascularity which we had associated with syphilis, but other areas appeared normal. These "doubtful" sections were put aside for later study and in some cases other portions of the placenta were sectioned. When data concerning the Wassermann reactions on many of the others and infants had accumulated, these "doubtful" sections were reviewed and it was found that in a considerable proportion of them the mother and infant were free from clinical syphilis and had negative Wassermann reactions. The slight deviations from the normal in these "doubtful" cases, therefore, were considered unimportant and such placentas classed as negative. Consequently, the placentas called "positive" were those showing well marked and characteristic changes. It is of interest that in every instance of this group in which the later examination of the infant could be made, the Wassermann reaction was positive. The sixteen placentas classed as negative in which the infants were later found to have syphilis, were reviewed by Dr. E. L. Opie who agreed that the characteristic changes of syphilis were not present in these sections.

All Wassermann reactions were carried out with 0.1 c.c. of inactivated serum with both the alcoholic and the cholesterolized antigen at incubator temperature. Attention has been called [3] to the occasional appearance of a positive reaction with cholesterolized antigen alone during pregnancy in women who are free from clinical syphilis. In certain cases this positive reaction has disappeared after the puerperium. On the other hand, many cases of proved syphilis give a positive reaction only with the cholesterolized antigen and the absence of clinical signs is no sure criterion of the absence of infection. While we believe that a + or a ++ reaction with this antigen in cord bloods is of little significance, our experience indicates that a strongly positive (+ + + +) reaction is rarely found except in patients with syphilis.

INCIDENCE OF SYPHILIS AMONG THE INFANTS EXAMINED

Of 1,095 pregnancies in the poor class in the group under observation, we were able to examine 389 infants at two or more months of age (Table 1). Physical examination and Wassermann test were made in every instance. In this group syphilis was diagnosed in twenty-two infants. Clinical evidence of syphilis was present in eleven infants at

3. Cornell, E. L. and Stillians, A. W.: The Value of the Wassermann Reaction in Pregnancy, J. A. M. A. **72**:551 (Feb. 22) 1919.
Ottenberg, R.: On the Reliability of the Wassermann Reaction, Arch. Int. Med. **19**:457 (March) 1917.

the time of examination. Each of the twenty-two infants gave a strongly positive Wassermann reaction in the serum. No doubtful reactions were encountered and all those giving a positive reaction were considered syphilitic even in the absence of any clinical evidence. The fact that one-half of the syphilitic infants showed no clinical evidence of the disease at the time of our examination illustrates the fallacy of basing the diagnosis as to the presence or absence of syphilis on the physical examination alone as has been done in some studies.

TABLE 1.—INCIDENCE OF SYPHILIS IN 389 INFANTS OF THE POOR CLASS

	White	Colored	Total
Total pregnancies of group	708	387	1,095
Infants examined after 2 months	206	183	389
Infants syphilitic	5	17	22
Per cent. syphilitic	2.4	9.3	5.65

In this group of 389 infants of the poor class, the total incidence of syphilis was 5.65 per cent. Classification according to race shows an incidence of 9.3 per cent. among the negroes and 2.4 per cent. among the whites.

THE RELATION OF PLACENTAL HISTOLOGY TO THE ESTABLISHED DIAGNOSIS IN THE INFANT

The diagnosis as to the presence or absence of syphilis in the infant was established in 389 instances (Table 1). In this group the histologic diagnosis of the placentas as to the presence or absence of syphilis agreed with the established diagnosis of the infant in 95.5 per cent. The lack of correspondence consisted entirely in finding no syphilitic change in the placenta in cases in which the infant had syphilis. In every instance in which the placenta was noted as showing syphilitic changes the infant was later found to have syphilis.

TABLE 2.—RELATION OF PLACENTAL HISTOLOGY TO ESTABLISHED DIAGNOSIS IN INFANT

Total of group studied	389
Infant normal—placenta negative	367
Infant normal—placenta positive	0
Infant syphilitic—placenta positive	6
Infant syphilitic—placenta negative	16
Agreement in whole group	95.5
Agreement in syphilitic group	27.3

That changes characteristic of syphilis of the placenta may be found, as has recently been claimed, in the absence of syphilis in the infant is extremely doubtful on theoretical grounds and has not been proved by the published facts. Considering the syphilitic cases alone the microscopical examination of the placenta failed to show evidence of syphilis in 73 per cent. In other words, of twenty-two syphilitic babies the placenta was positive in six instances.

THE RELATION OF THE WASSERMANN REACTION ON PLACENTAL CORD BLOOD TO THE ESTABLISHED DIAGNOSIS IN THE INFANT

A total of 247 placental cord blood specimens was examined in cases in which the infant was examined at 2 or more months of age. The results of the Wassermann reaction on these specimens were not so clear but what a certain amount of discussion is necessary, inasmuch as ten doubtful reactions occurred. Table 3 shows the actual results obtained.

TABLE 3.—RELATION OF WASSERMANN REACTION ON PLACENTAL CORD BLOOD TO THE WASSERMANN REACTION ON THE BLOOD OF THE INFANT AFTER TWO MONTHS OF AGE

	No. of Cases	Maternal Blood		Cord Blood at Birth		Infant's Blood After 2 Months	
		Chol.	Alc.	Chol.	Alc.	Chol.	Alc.
A*	228	.....	.....	—	—	—	—
B*	5	.....	.....	++++	++++	++++	++++
C*	4	.....	.....	—	—	++++	++++
D	1	++++	++++	++++	—	++++	++++
E	1	++++	++	++++	—	++++	++++
F	1	++++	—	++++	—	—	—
G	1	++++	—	++++	—	—	—
H†	1	++++	++++	+++	—	—	—
I	1	++++	—	++	—	—	—
J	1	++++	++++	+	—	—	—
K	1	+	—	+	—	—	—
L	1	—	—	+	—	—	—
M†	1	++++	++++	+	—	—	—

* While the Wassermann on the maternal blood was performed on about 90 per cent. of this group and a few positive reactions found, they have not been tabulated since our interest is chiefly in the relation of the Wassermann on the cord blood to the presence of the disease in the infant.

† Mother treated during pregnancy.

In 237 instances decisive results are shown (Groups A, B and C). A one plus reaction with cholesterolized antigen (J, K, L and M) is scarcely worthy of serious consideration as a positive reaction. There remain six more or less doubtfully positive reactions with fetal cord blood. Of these two of the infants had syphilis and four had not. If one may disregard the Wassermann reaction of less than four plus with cholesterolized antigen the agreement between the Wassermann reaction on the fetal cord blood and the diagnosis in the infant was 97.6 per cent. Considering the syphilitic infant group alone, syphilitic infants give a positive Wassermann reacton in their cord blood at birth in 63.6 per cent. when four plus reactions with the cholesterolized antigen are included and in 45.5 per cent. when these reactions are excluded. In all instances in which the fetal cord blood gave a positive reaction with alcoholic antigen the infant was later shown to have syphilis.

ESTIMATE OF THE INCIDENCE OF SYPHILIS IN THE POOR CLASS

It is noted above that of 389 infants examined of the poor class (Table 1) there was found an incidence for syphilis of 5.65 per cent.

for the whole group, 2.4 per cent. for the white race, and 9.3 per cent. for the colored race. To a certain extent this was a selected group in that it includes only those who would submit to examination. The number of syphilitic infants was small so that a difference of one or two cases in the racial subgroups would make distinct changes in the percentage incidence for each race, though not so much difference in the total incidence. It is not very surprising then that the study of a larger group indicates slightly different percentage incidence in the racial subgroups.

Of the 2,030 cases of this report, 1,095 were of the dispensary or poorer class. On the basis that the number of placentas showing syphilitic changes is equivalent to 27 per cent. of the total number of syphilitic offspring (Table 2) we find that in the infants of this group there was an estimated incidence of 6.4 per cent. On the basis that syphilitic infants give a positive Wassermann reaction on their cord blood in 63.6 per cent. of the cases we find that the incidence of infantile syphilis in this same group was 6.3 per cent. Classified

TABLE 4.—ESTIMATED INCIDENCE OF HEREDITARY SYPHILIS IN THE POOR CLASS

Placentas		Fetal Cord Blood	
Total number placentas examined	1,095	Total specimens examined	672
Number of placentas negative	1,076	Negative Wassermann	645
Number of placentas positive	19	Positive Wassermann (all antigens)	17
Estimated total of positive cases (see Table 2)	70	(4+ cholesterol only)	10
Estimated per cent. of positive cases.	6.4	Total positive Wassermann	27
		Estimated total positive cases (see Table 3)	42
		Estimated per cent. of positive cases	6.3

according to race by both methods of estimation we find 1.8 per cent. of the white infants and 15 per cent. of the colored infants syphilitic.

It is observed that the total incidence in the group of 1,095 patients as estimated from the placental examination (6.4 per cent.) corresponds very closely to that estimated from the Wassermann on the cord blood (6.3 per cent). It is also observed that the incidence estimated by these two methods (6.3 and 6.4 per cent.) corresponds very closely to the established incidence (5.65 per cent.) in a smaller group of 389 of the same social class. This fact tends to confirm the reliability of the methods of estimation and establishes the justification for applying either or both methods of estimation among other social classes.

ESTIMATION OF THE INCIDENCE OF SYPHILIS IN THE WELL-TO-DO SOCIAL CLASSES

Of the 2,030 cases of this report, 935 were classed as private patients. These patients were able to pay a physician's fee and private room rates in a hospital and for that reason have been considered as belonging to the well-to-do classes. Of the entire number of 935

placentas, not a single placenta showed sufficient evidence of syphilis to warrant a positive diagnosis of this infection. In this same group 455 fetal cord bloods were examined. The results of the Wassermann reaction on the blood are tabulated in Table 5.

TABLE 5.—WASSERMANN REACTION ON FETAL CORD BLOOD IN 455 CASES IN THE WELL-TO-DO CLASSES

No. of Cases	Wassermann Reaction			Remarks
	Cholesterol	Alcoholic		
449	—	—		
0	++++	++++		
1	++++	Not done	}	Regarded as positive
2	++++	—		
2	++	—	}	Regarded as negative
1	+	—		

From Table 5 it is seen that there is not a single cord blood which gives a positive Wassermann reaction with the alcoholic antigen and, therefore, not a single definite case of syphilis in the whole group. Regarding the three cases with four plus reaction with the cholesterolized antigen as cases of possible syphilis the number of cases of hereditary syphilis in this group may be estimated (Table 3) at five cases, or 1.1 per cent. Such a figure must be regarded as a maximum for this group. It is of interest to note that in one case in which the placental examination was negative and in which no fetal cord blood was obtained for examination the mother's Wassermann reaction was strongly positive. That some syphilis occurs in the social classes under consideration there can be no doubt, but the results here presented indicate that the estimates of the frequency of syphilis in these classes are much exaggerated and need revision. The frequency of hereditary syphilis in the upper social classes as estimated in this study does not exceed 1 per cent., and probably is less than this figure.

RACIAL AND SOCIAL SUBDIVISIONS OF THE POPULATION OF ST. LOUIS

According to the fourteenth census (1920), St. Louis has a population of 772,897. Of this number 69,854 (9 per cent.) are negroes, 702,615 (91 per cent.) are of the white race and 428 (0.05 per cent.) are of other races. The census also shows that the number of families in St. Louis is 190,640. The number of families by race and color is not available. Assuming that the racial distribution by families is approximately in the same proportion as the racial distribution of individuals, we find 173,386 white families, 17,138 colored families and 116 families of other races.

The division of the population into social classes on a financial basis has been estimated from information obtained from the St. Louis

assessor for the Missouri state income tax. With a very few minor exceptions the exemptions for the state tax are the same as those for the federal income tax, i. e., $2,000 for a family of two with $200 additional for each dependent. For the year 1920, 75,000 individuals in St. Louis made state income tax returns. An expert in the office of the assessor has estimated that there are approximately 10,000 additional individuals who have an income above the exemption level. These 10,000 consist of 3,000 government employees who are exempt, of 2,000 railway employees who for two months of the year were federal employees and whose salary for ten months did not exceed the exemption, and finally of approximately 5,000 individuals who should have made tax returns but did not. Thus there is probably a total of about 85,000 individuals in St. Louis having an income which would place them financially in the well-to-do social classes.

In order to determine what proportion of individuals making tax returns represented families, the assessor's office tabulated for us 1,000 returns taken at random. Of those tabulated, it was found that 46 per cent. of the returns represented families and 54 per cent. single individuals. Applying this proportion to the entire number, we find that 39,000 families received annual incomes of $2,000 or over. A family with an income of less than $2,000 a year could scarcely afford a private room in a hospital and a physician's fee for childbirth, and it seems to us that a family with an income of more than $2,000 a year could well be considered as belonging to the well-to-do class. So few colored individuals receive sufficient income to place them in the middle or upper class that for the purposes of this study they may be ignored.

To summarize the above statistics and estimates, we find that there are in St. Louis 39,000 white families of the well-to-do class, 134,000 white families of the poorer class and 17,000 colored families.

ESTIMATE OF THE AMOUNT OF HEREDITARY SYPHILIS IN ST. LOUIS

Having determined the frequency of syphilis in the infant at the time of birth in small groups of different social classes, and the number of families in St. Louis of these same social classes we may estimate the total amount of hereditary syphilis in the city at the time of birth. Not all families, of course, produce offspring. Sterility is generally conceded to occur in about 10 per cent. of all marriages, the percentage being somewhat higher in the upper than in the lower social classes. Though syphilis may be a cause of childless marriages, it plays no appreciable part in sterility, as has already been pointed out. In order to arrive at the number of families who have or will have offspring, we may deduct from the totals given above about 10 per cent. Thus we

have 35,000 families of the well-to-do white class, 121,000 families of the poorer white class and 15,500 colored families. Table 6 shows the application of the incidence of hereditary syphilis already found in different classes at the time of birth to the total number of child bearing families of those same classes.

TABLE 6.—ESTIMATED INCIDENCE OF HEREDITARY SYPHILIS IN ST. LOUIS AT THE TIME OF BIRTH

	Number of Families	No. of Families With Syphilitic Children	Incidence in Class, per Cent.
White families of the better class	35,000	350	1.0
White families of the poorer class	121,000	2,178	1.8
Colored families	15,500	2,325	15.0
Total	171,500	4,853	2.8

It seems desirable to call attention to the fact that not all syphilitic mothers have syphilitic offspring, and that, therefore, the number of infants with syphilis represents but a part of the syphilitic married women. In the group of 389 in which the infant was examined, and in those of this group in which the infant did not have syphilis, there were eight mothers with strongly positive Wassermann reactions and thirteen with a 4 plus Wassermann reaction with cholesterolized antigen. In addition to these there were several mothers who were syphilitic, received treatment during or prior to the pregnancy and who gave birth to nonsyphilitic offspring. Forty-six mothers were not examined; forty-five of these were mothers of babies who did not have syphilis.

The fact that we have found about 2 per cent. of the infants born in the poorer class to be syphilitic does not conflict in any way with the well founded figure of 10 per cent. for married women of this same class.[2] Similarly our figure of 1 per cent. for infants of the better class is lower than that found by Cornell and Stillians [3] for pregnant women of the same class.

The results given in this paper differ somewhat from those given in a preliminary report [4] on the first 1,000 cases. This is due, in part, to the fact that a larger number of cases gave slightly different results and in part to the fact that further experience in histological examination of the placenta has led us to class as negative some of the placentas which were at first diagnosed as showing syphilitic changes. We realize that though the total amount of material studied by us was fairly large, certain groups in that material are too small to allow us to draw any far reaching conclusions on a statistical basis.

4. Jeans, P. C., and Cooke, J. V.: A Study of the Incidence of Hereditary Syphilis, Tr. Am. Ped. Soc. **32**:135, 1920.

SUMMARY AND CONCLUSION

A study of the placenta and the Wassermann reaction on the cord blood was made on a series of 2,030 unselected infants in St. Louis. By examining the blood of 389 of these infants after 2 months of age, it was determined that the proportion of cases of hereditary syphilis that could be certainly diagnosed by placental examination alone was 27 per cent. while from the Wassermann reaction on the cord blood, 63.6 per cent. of the cases could be recognized. By applying these two methods to the entire series the number of cases of hereditary syphilis in the whole group was determined. The incidence of hereditary syphilis established by this method is 15 per cent. in the colored race, 1.8 per cent. in the poor of the white race and less than 1 per cent. in the well-to-do social classes. By applying these figures to the entire population of St. Louis, it is estimated that the incidence of hereditary syphilis at birth in this city is 3 per cent., of which the colored population, although only 9 per cent. of the total, contributes approximately half the cases.

We wish to express our thanks to Dr. A. C. Kirby who assisted greatly in supervising the collection of our material and in the keeping of our records. Also great credit is due to the municipal nurses organization of St. Louis in their untiring efforts to bring to us the infants we desired to examine. Their records show them to have made about 4,000 visits in connection with the return of these infants.

CLINICAL DEPARTMENT

CALCIFICATION OF THE SKIN IN A CHILD*

JOHN LOVETT MORSE, A.M., M.D.
Professor of Pediatrics, Harvard Medical School
BOSTON

REPORT OF CASE

History.—Stella R., the child of poor and very ignorant Polish parents, was born at full term and was normal at birth. She was nursed for eight months and was then given the family diet. She had an attack of diarrhea when 10 months old. She walked at 13 months. When about 22 months old, she was sick for a week with what was called influenza. About a month later she fell from a chair and soon after ceased to walk. She was admitted to the Children's Hospital in March, 1919, when a little more than 2 years old. The diagnosis at that time was postinfluenzal peripheral neuritis. Her general nutrition was fair and she was very slightly rachitic. There was a little eczema in both axillae and behind the ears. The tonsils were enlarged. The hemoglobin was 59 per cent. (Sahli); the white count 8,400, and the tuberculin test was negative.

In May, 1919, she was treated in the Medical Outpatient Department, at which time it was noted that there was an indurated area, the size of a small lemon, dark purple-red in color, but not hot or tender, in the left buttock. This was supposed to be an absorbing subcutaneous abscess.

In August, 1919, she was treated at the Boston Dispensary for ulcerations with indurated edges in the folds of both axillae and on both sides of the chest. These ulcerations were thought to be due to abscesses which had broken down. The extremities were normal at that time.

She was cared for at the Convalescent Home during the late summer and autumn of 1919. The Wassermann test, done at that time, was negative.

She was then lost sight of for nearly a year. Her tonsils and adnoids were removed at the Children's Hospital, Oct. 27, 1920, and Nov. 15, 1920, a large furuncle of the left arm was opened in the Surgical Outpatient Department.

Present Illness.—She was admitted to the wards of the Children's Hospital Nov. 24, 1920, when 3½ years old, having been sick with some respiratory condition for about a week.

Examination.—She was poorly developed, badly nourished and extremely dirty. There was a dermatitis of the scalp. The teeth were very bad. The tonsillar fossae showed necrotic tissue left from the tonsillectomy. There were the remains of a rosary. There was a moderate bronchitis. The heart was normal. The liver was palpable 3 cm. below the costal border in the nipple line. The spleen was not palpable. The extremities were normal. There was some dermatitis about the neck, apparently the result of local irritation. The cervical glands were slightly enlarged. There were areas of induration at the borders of both axillae and at the left elbow. There were large areas of induration in the upper inner thighs, in the buttocks and in small areas in the popliteal spaces and in the calves of both legs. The induration was very firm and apparently in the skin and subcutaneous tissues. In some places there were numerous, small, hard nodules scattered through the indurated areas. These areas were apparently a little tender. The father stated that he first noticed these areas of induration about a year before. She weighed 21½ pounds.

* Received for publication, June 21, 1921.
* From the Medical and Pathological Services of the Children's Hospital.
* Read before the American Pediatric Society, June 4, 1921.

Roentgen-Ray Examination.—The roentgenograms of these indurated areas showed a most remarkable picture, as wherever these indurated areas occurred it looked as if the tissues were filled with fine shot. The only plausible explanation seemed to be that these indurated tissues were undergoing calcification.

Blood Examination.—The blood showed hemoglobin, 80 per cent. (Talquist); red corpuscles, 4,520,000; white corpuscles, 23,600; small mononuclears, 43 per cent.; large mononuclears, 1 per cent.; polymorphonuclear neurtrophils, 56 per cent. The red cells were normal in size and shape. The platetets were normal in number.

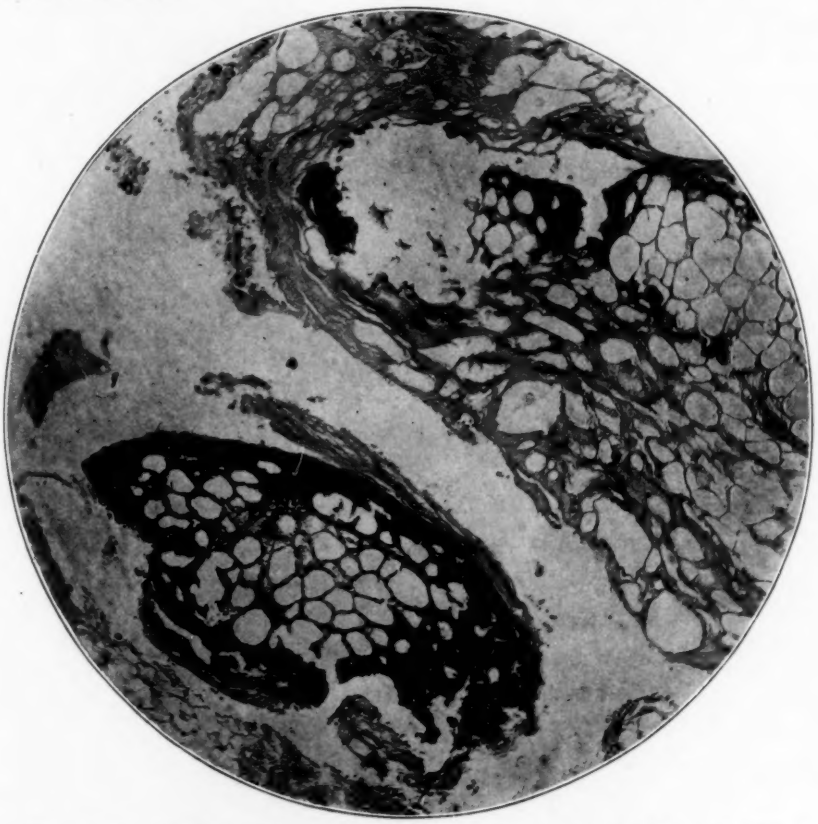

Fig. 1.—Low power photomicrograph showing two fat lobules with deposit of lime in and around fat cells. The lime appears a dense black in the photograph.

Urine Examination, Etc.—The urine was normal on repeated examinations. The stools showed no evidence of indigestion. The Wassermann test on the blood was negative. The tuberculin test was negative.

Microscopic Examination.—A small piece of tissue, including fat and fascia was removed from the outer side of the right thigh December 1 by Dr. James S. Stone, and Dr. S. B. Wolbach's report on this tissue was as follows:

Sections through the nodule show on one side normal fascia. The fat tissue everywhere is largely replaced by fibrous tissue although there are a few almost normal fat lobules, some containing areas of lymphoid and plasma cell infiltration and others a degeneration of fat cells without cellular reaction resulting in the deposit of a lightly eosine staining

Fig. 2.—Roentgenogram of legs.

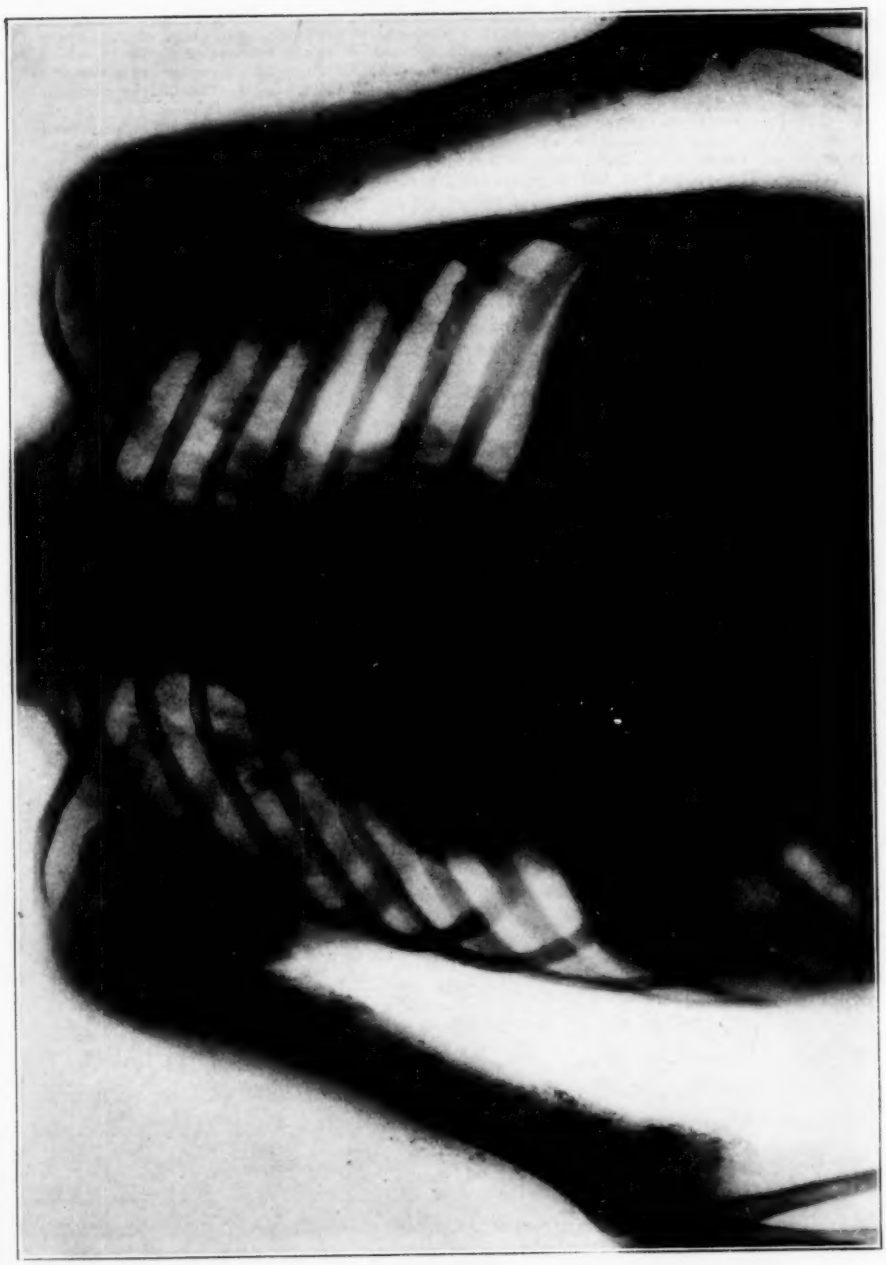

Fig. 3.—Roentgenogram of chest and arms.

refractive material. Many fat lobules contain a deeply basic stained coarsely granular material completely replacing fat cells or deposited upon the periphery of fat cells. The deposit of basic staining material interpreted as lime salts has evidently followed the formation of the refractive material left by degenerated fat cells. Surrounding and penetrating into the lime salt deposits is dense hyaline connective tissue without giant cells. There is no bone formation. The bulk of the tissue consists of dense connective tissue in which are irregular areas of dense lime deposits and the hyalin matrix, without recognizable remains of fat lobules. A rare fat lobule shows the outline of fat cells, each surrounded by granular calcified material with occasional cells containing a similar deposit in the interior.

The process is interpreted a primary degeneration of fat followed by calcification and repair by avascular organization without giant cell formation. An unusual feature is the absence of evidence of the formation of fatty acid crystals usually to be seen in fat necroses. The product of the degenerated fat seems in this case to be a homogeneous hyaline material in which the lime deposited.

Diagnosis.—Necrosis of subcutaneous fat with atypical sequence and calcification. Etiology unknown.

Clinical Course.—She remained in the hospital for six weeks. During this time she had very little fever, gained in weight and improved in every way. She then contracted scarlet fever and was discharged to the South Department of the Boston City Hospital.

DISCUSSION

The history in this case suggests strongly that the changes in the skin were due to infection. The histology shows no evidence, however, that an infectious process was the cause of the lesions in the subcutaneous fat.

The microscopic appearances resemble in many particulars the fat necroses found in the abdominal cavity in acute pancreatitis where the lesion is, of course, due to the action of a lipolytic ferment. In spite of the difficulty in accounting for the presence of such a ferment in the subcutaneous tissue, such a possibility must be considered in this instance.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE OF 1920 ON GENITO-URINARY CONDITIONS IN CHILDREN *

LEWIS WEBB HILL, M.D.
BOSTON

ABDOMINAL PAIN IN GENITO-URINARY DISEASES

According to Cecil [1] the classical condition of pain, beginning in the lumbar region, radiating to the lower abdomen, to the genitalia and to the inner side of the thighs, is the most typical picture of renal pain, but variations from it are common. Pain arising from the kidney or ureter is often purely abdominal in type. The localization of the pain is often in the upper abdomen beneath the costal border, or in the neighborhood of McBurney's point. Stone and hydronephrisis are the two most common genito-urinary conditions which are characterized by pain. In 28 per cent. of Cecil's cases of stone, the pain was purely abdominal, and in a number of these it was so misleading as to lead to abdominal operations. In a large percentage of cases of hydronephrosis also, the pain is almost entirely abdominal, which makes the diagnosis difficult, as the urine is very likely to be normal.

KIDNEY TUMORS

Fraser [2] gives a most thorough discussion of kidney tumors. Tumors of the kidney during the first five or six years are most likely to be adenosarcomas. Out of 15,000 outpatient cases only seven kidney tumors were seen. The most striking symptom is a gradual increase in the size of the abdomen. The child may seem quite well, however, and the mother brings him to the doctor not because he has any symptoms, but because she has noticed that his abdomen is large.

With suddenness, the symptoms alter, the abdominal swelling increases rapidly in size, the superficial veins over the abdomen become prominent, and there is loss of flesh and weight. No urinary symptoms are ordinarily apparent. The tumor at its beginning is encysted, and it is only after a certain period has elapsed that it acquires the characters of a highly malignant sarcomatous type. With the appearance of the sarcomatous change the picture alters, the tumor grows more

*Received for publication May 23, 1921.

1. Cecil: J. A. M. A. **75**:1239 (Nov. 6) 1920.
2. Fraser: Edinburgh M. J. **24**:372 (June) 1920.

rapidly, general wasting appears, and it is now that pain may begin to be felt. It is imperative to operate before the appearance of this stage. It is unlikely that the affected kidney has any physiological activity whatsoever.

TUBERCULOSIS OF THE KIDNEY

According to Braasch,[3] when tuberculosis of the kidney occurs in children (although it is rare), it is usually in conjunction with tuberculosis disseminated in other tissues. Nephrectomy should not be done at the first onset of symptoms, and it is not advisable unless it is quite evident that the active tubercular focus is confined to the kidney. Evidence of tuberculosis in other parts of the body (healed or active) was found in 244 of 346 patients (71 per cent.) operated on in the Mayo clinic for tuberculosis of the kidney. Pulmonary tuberculosis is one of the most common co-existing forms of tuberculosis, but is usually found in a healed form. In only 6.4 per cent. of 535 cases of renal tuberculosis was there any well marked evidence of tubercular adenitis. A moderate degree of anemia was noted in about 25 per cent. of the cases. This is probably caused more from the general debilitating effects of the disease than from loss of blood in the urine. The operative mortality was 1.3 per cent. Approximately 80 per cent. of the operated patients will recover, and a complete cure may be expected in 60 per cent.

CALCULUS OF KIDNEY

Hinman [4] reports a case of multiple renal stones in a child, aged 8 months. Suddenly, without apparent cause, there was complete retention of urine for three days, with great suffering, which subsided with the passage of a large amount of urine. Six days later a stone the size of a pea was passed, without trouble. The next day another one was passed, and the pain was so severe that convulsions occurred. A month later three similar stones were passed. The urine showed a faint trace of albumin and a few white and red blood cells. On ureteral catherterization the left urine was purulent and loaded with bacilli, the right negative. Left ureteronephrectomy was performed and recovery was uneventful.

ORCHITIS IN MUMPS

The paper of Wesselhoeft [5] is probably the most complete that has been written on orchitis and consists essentially of a review of the literature. In his 8,153 collected cases of mumps there was testicular involvement in 1,463, giving a percentage of 18 per cent. He

3. Braasch: Am. J. M. Sc. **159**:8 (Jan.) 1920.
4. Hinman: J. A. M. A. **76**:237 (Jan. 22) 1921.
5. Wesselhoeft: Bost. M. & S. J. **183**:425, 458, 491, 520, 1920.

recommends as treatment cold compresses during the acute stage, and in many cases incision through the tunica vaginalis and multiple incisions of the tunica albuginea to relieve the pressure and to stop the pain, which in experienced surgical hands is a safe and logical procedure. Atrophy of one or both testicles takes place in 55 per cent. of all cases of orchitis from mumps.

Ballenger and Elder [6] believe that it is not necessary that so many testicles should be atrophied after mumps. The destruction is probably caused by two things: (1) The local toxic action of the organisms of mumps; (2) the pressure necrosis due to the inelastic tunica albuginea preventing the testicular substance from swelling in response to the inflammation present. Orchitis follows mumps in from 10 to 25 per cent. of the cases, and in about one half of these atrophy results.

The rational plan of treatment is to incise the tunica albuginea and relieve the pressure. This must be done early in the disease before too much pressure has developed. It is not a complicated procedure, and carries with it but little danger if done properly. It may be the means in many cases of saving the function of the testicle.

PYELITIS

The urine, especially of girls, may contain normally a few white blood cells, and it is often rather difficult in the diagnosis of pyelitis, to tell whether or not the number of cells is greater than normal.

Dyson [7] believes that the ordinary methods of roughly estimating the amount of pus in urine are too inaccurate, and has developed a method which he believes is better. He counted the number of cells per cubic millimeter in an ordinary white blood counter, using the urine as it was passed, and found that the normal for boys was 2 or 3 cells per cubic millimeter; for girls, 3 or 5 cells. (This method of counting seems rather an unnecessary refinement, and is not so accurate as it appears at first glance, for no cognizance was taken of the amount of urine that was passed; counted in this way, a concentrated urine would naturally contain a good many more cells than a dilute urine.—L. W. H.).

Shohl and Deming [8] have made a careful study of the action of hexamethylenamin.

The simple chemical change from hexamethylenamin to formaldehyd is slow and gradual, and even with a uniform excretion, the longer the drug is allowed to accumulate in the bladder, the greater becomes its concentration and the more complete its conversion. This

6. Ballenger and Elder: J. A. M. A. **75**:1257 (Nov. 6) 1920.
7. Dyson: M. Clinics. N. America **3**:1547, 1920.
8. Shohl and Deming: J. Urology **4**:419, 1920.

necessary time factor completely nullifies the value of the drug as an internal urinary antiseptic in many urinary conditions. Polyuria and frequent urination prevent this accumulation, and the constant outflow from the kidney, except in hydronephritic cases, accounts for the fact that the drug is of little, if any, value at the level of the kidney. It is, furthermore, valueless for urethral antisepsis, no matter what the infection. The amount of formaldehyd liberated from the hexamethylenamin is dependent upon the acidity of the urine. For each hydrogen ion concentration, a definite amount can be expected in a definite time. From 60 to 75 per cent. of the hexamethylamin given is excreted in the urine. The change to formaldehyd progresses slowly, and in two hours only 5 per cent. has been converted in the most acid urine that can be excreted. With a patient taking 4 gm. hexamethylenamin every day, and passing 1.5 liters of urine containing 75 per cent. of the hexamethylenamin taken in, there would be 2 gm. per liter, or a 1 : 500 dilution, and if 5 per cent. of this were converted to formaldehyd, the concentration of formaldehyd, would be 1 : 10,000, enough to kill most organisms. It is thus seen that even if only a comparatively small amount of the hexamethylenamin ingested is converted to formaldehyd in the urine, the concentration is enough to be efficient as a urinary antiseptic.

Morse [9] reports an unusual case of long standing pyelitis with marked diminution of renal function. A girl, aged 10 years, had had pyelitis for four years, but was in fair condition, except for moderate anemia. She was treated with large doses of soda bicarbonate, during which treatment she developed severe spasmophilia and nearly died. A few days later, after the spasmophilia had cleared up, treatment with hexamethylenamin and acid sodium phosphate was begun. After a few days of this treatment she again developed spasmophilia. Various tests for kidney function were then tried, and it was found that she had a marked fixation of gravity at a very low level, a considerably increased blood urea, and excreted only a trace of phenolsulphonephthalein in two hours. These tests, which showed that the kidneys possessed very little excretory power, gave a probable explanation for the spasmophilia, in that they were unable to excrete the sodium salts which had been given, and the consequent retention of a large amount of sodium increased nervous irritability enough to cause the symptoms of spasmophilia.

ALBUMINURIA

Barach [10] made observations on the urines of fifty-seven normal young men before and after daily baseball and track work. Eighty-five

9. Morse: New York M. J. **112**:965 (Dec. 18) 1920.
10. Barach: Am. J. Med. Sc. **159**:398, 1920.

per cent. of all the urines after exercise showed increased acidity (hydrogen ionization); 77 per cent. showed albumin. After track work, sixteen showed albumin, two none; after baseball, twenty-six had albumin and ten none. After track work, 71 per cent. had casts and a few had red blood cells. After baseball, these were found in only 23 per cent. After a Marathon race (25 miles) albumin, casts and red blood cells were found in the urines of all these who finished.

Lee,[11] in charge of the health of the students of Harvard College, reports the results of urine examination on 5,000 cases. Five per cent. of the urines examined showed albumin (a very definite ring with nitric acid in all cases), and of this 5 per cent., only 15 per cent. showed casts or cells. Among the best athletes, who represented a special type of physical fitness, there was albuminuria in only 1 per cent. and it was three times as frequent among those students who had poor posture as among those who had good posture. It was found that there was a tendency for the albuminuria to clear up, and it was much more frequent among the freshmen than the upper classmen. As far as could be ascertained none of the men showing albumin who were not at the time thought to be suffering from nephritis, have since developed it (over a period of five years). "Albuminuria has been hitherto recognized as perhaps the most common sign of kidney damage. It has been noted that it occurs in fever and after physical exertion. The literature also contains a good many reports of what is usually called albuminuria of adolescence, or physiologic or orthostatic albuminuria. Even persistent albuminuria is not incompatible with a clear bill of health, especially when it is absent after rest in bed and is present in varying amounts depending upon the amount of physical exertion. Albuminuria in young men has been the cause of much needless alarm."

Parmenter,[12] who is associated with Lee, has continued his studies.

During the last college year (1919-1920) 513 freshmen in Harvard College, of an average age of 18, were examined. Forty, or about 8 per cent. showed albumin. The examination of the sediment in all cases showed nothing more than an occasional cylindroid or a few squamous cells. In a second examination of thirty-four of these, some weeks afterward, sixteen still persisted in showing albumin. In the third examination two weeks later, six still showed albumin. This would indicate that most of the cases were transient albuminurias, which might, perhaps, be designated as functional. A constant number of young men of 18 will show albumin in the examination of a single specimen of urine, but with each reexamination the individuals making up this number will vary. Such individuals do not fall into any par-

11. Lee: M. Clinics. N. America **3**:1059, 1920.
12. Parmenter: Boston M. & S. J. **83**:677, 1920.

ticular postural group, nor do they have any recognized type of bodily defects. In fact, all the thirty-four men cited were physically sound. The six men who showed albuminuria on repeated examination were found to have albumin only in specimens taken during the day, and none in the early morning specimens. These men had, therefore, what is called "orthostatic" or "postural" albuminuria. There was also in five of the six cases a nervous instability and a physical condition below par. Persistent albuminuria cannot be regarded as a normal finding, even if the actual significance is trifling. The men on the various freshmen athletic teams showed about the same percentage of transient albuminuria as the class as a whole. The albuminurias in all the athletes were of the transitory type, and none were orthostatic. This again seems to lessen the importance of the transitory type. "It would seem justifiable to disregard the transitory type of albuminuria except as an index of physical ability during a definite time of life. The orthostatic type, on the other hand, while indicative of no physical deficiency serious enough to bar the individual from athletics, seems worthy of close observation."

NEPHRITIS

Etiology.—Jones [13] reports a case of acute nephritis caused by soaking an ulcer of the foot in a strong solution of compound solution of cresol, and then applying a bandage soaked in the same. (Any drug of the phenol group is likely to cause nephritis if absorbed. I have recently seen a case caused by the swallowing of a teaspoonful of sulphonaphthol, and one caused by absorption of turpentine fumes from paint.—L. W. H.). According to Christian [14] we know little, in the exact sense, of the etiology of nephritis, though the view is receiving increasing support that many cases have their primal cause in an infection of bacterial nature, more frequent of the streptococcus group. Even granted, however, that organisms such as this originate the renal disturbance, we are not helped much in the matter of treatment because, in the case of the known nonrenal streptococcus lesions we are able to treat only by elimination or drainage of the focus of infection and can do little, if anything, toward counteracting the toxic substances that are produced and distributed to the body organs. If actually resulting from an infection, the chronic renal lesion presents itself months or years afterward, too late to be helped much by removal of the focus of infection, even if still present. In other words, in the earlier, easily treated stages of the infection it may pass unrecognized, or what happens more frequently, there is nothing to indicate the beginning of a lesion in the kidney which slowly and gradually will develop into a

13. Jones: Boston M. & S. J. **182**:68, 1920.
14. Christian: J. A. M. A. **74**:1615 (June 12) 1920.

recognizable nephritis. In the later stages, when the renal lesion is easily recognized, the focus is no longer existent, or if present, its removal can change but little the renal damage already done. Christian has been struck, in his own experiences, with the relatively few cases of chronic nephritis that seem to have arisen in direct sequence to a demonstrated infection or infectious disease; most of these have belonged to a rather distinctive group of cases, progressing rapidly to a fatal issue, and perhaps better thought of as subacute than as chronic nephritis.

Day and Clark,[15] working in Egypt, have investigated the etiology of nephritis which occurs without apparent cause. Many cases of nephritis occur secondary to acute infections. They base their experimental work on the assumption that cases of "idiopathic" nephritis are due to some unrecognized infection of the kidney and that the causative organisms are present, with the products of inflammation, in the urine and in the kidney itself. As a result of their work, they believe that the toxic effect of nephritic urine depends chiefly on the presence or absence of bacteria. The frequency with which pure cultures of Gram negative bacilli were obtained from the urine is significant, they believe. The cultural characteristics of the organisms were those of the colon-typhoid group, and the investigators believe that many cases of nephritis may be due to bacteria of intestinal type.

Classification.—Foster,[16] says that classifications based purely on anatomical changes in an organ whose physiology is quite obscure help not at all therapeutically. "Today there is no consensus of opinion even among physiologists as to the specific function of the glomerulus or the tubule."

Christian,[17] says that a structural consideration of renal lesions helps but little in treatment, and clinical classification cannot be accurately correlated with structural classification.

Hill [18] states that the classification of chronic nephritis, whether it be in the child or in the adult, has always offered considerable difficulty. The variations in the clinical picture which may be presented are many, depending upon the amount and kind of damage that has been done, and the stage of the disease in which the patient may be at the time. "The older pathologic classification has not been satisfactory for practical purposes, is gradually being done away with, and is being replaced by a simple clinical classification. For practical purposes we may divide cases of chronic nephritis in children into two broad groups: (1) ordinary chronic nephritis, further subdivided into the mild and

15. Day and Clark: Lancet **2**:546, 1920.
16. Foster: Med. Clinics. N. America **4**:1, 1920.
17. Christian: J. A. M. A. **74**:1615 (June 12) 1920
18. Hill: J. A. M. A. **75**:596 (Aug. 28) 1920.

the severe cases, and (2) chronic nephritis with infantilism, or 'chronic interstitial nephritis,' as it is more often called—an excessively rare condition in children."

Miscellaneous.—Baehr and Larde [19] in a series of twenty-seven cases of subacute streptococcus endocarditis noted 9 who died with uremia. At necropsy there were two types of renal lesions found; (1) acute glomerulonephritis; (2) chronic diffuse nephritis. They believe, contrary to the general opinion, that the streptococcus was not the direct cause of the lesions, as they did not find streptococci in the glomeruli. However, as they had only two cases of acute glomerulonephritis, this opinion is not supported by much evidence.

Stevens and Peters [20] describe thirty-six cases of what they call "urinary tract purpura." It is a condition with an acute onset, a temperature of irregular type, general febrile symptoms, gross hematuria, frequency of urination and dysuria. No suggestion as to predisposing factors is likely to be found in the history. The striking thing about this series of cases was that they showed the general appearance of an acute infection, but that despite the hematuria, the common signs and symptoms of nephritis (edema, clyindruria, high blood pressure, etc.) were noticeably lacking. Many patients had severe dysuria, and the hematuria was usually so great as to make the urine appear bloody macroscopically. The acute stage lasted from three to fourteen days. All but one patient showed casts at some time, although they were not numerous, and in one case red blood cells were observed in the urine as late as the sixty-third day after onset. The phenolsulphonephthalein test showed a definite lowering from 13 to 50 per cent. Catheter specimens of the urine were cultured in thirteen cases. Staphylococci were recovered four times, streptococci once and the remaining specimens were sterile. The staphylococci were thought to be contaminations. Multiple fresh hemorrhages in the bladder mucosa were observed, and bloody urine was seen coming from the ureteral orifices but at no time was blood seen oozing from the bladder mucosa. The consistent presence of a few casts in the urine and the reduction of the phenolsulphonephthalein output seemed to be evidence enough to justify the assumption that a definite renal lesion was present. On the other hand, the picture differs very widely from that of ordinary nephritis, as edema, dyspnea, and uremic manifestations were lacking. The temperature and associated symptoms gave the authors the impression of a general toxemia, probably of infectious origin, and the bleeding from the kidney they look on as a urinary tract purpura.

19. Baehr and Larde: J. A. M. A. **75**:789 (Sept. 18) 1920.
20. Stevens and Peters: J. Urology **4**:1, 1920.

(These cases resemble very closely the most common type of nephritis in children, "acute hemorrhagic nephritis," in which there is marked hematuria, but where the general picture does not correspond to the older textbook descriptions of acute nephritis. In the textbooks little will be found concerning this type of renal lesion, but in the last few years, the periodical literature contains many references to it, and case reports. This type of nephritis (for it is a true nephritis) is probably associated in some way with the streptococcus toxemia and the chief lesions are probably in the glomeruli, which is the reason why casts are so few in the urinary sediment, and why edema is often lacking. To a pediatrist such cases as have been reported by Stevens and Peters (in adults) present no unusual features, and represent the common type of nephritis seen.—L. W. H.).

Olwens and Moog [21] have studied the size of the heart in acute nephritis. In the early stages involvment of the heart was found to be the rule. This can be clearly demonstrated only by roentgen-ray. This early change in the heart is due to a combination of hydropericardium and acute dilatation. It can be compared to the hydrops of other organs, and may arise or disappear very quickly. The hypertrophy of the left ventricle does not come until later, after several weeks, and is associated with the subacute or chronic stage.

Hill [22] discusses what he calls "mild chronic nephritis" in children. Chronic nephritis in the child may present a totally different picture from chronic nephritis in the adult, and may be extraordinarily mild in many cases. The child is brought to the doctor complaining of lack of appetite, loss of energy, failure to gain in weight, slight anemia, etc., and nothing essentially abnormal is found, except a moderate degree of albuminuris, with, perhaps, a few blood cells or casts in the urinary sediment. The heart is not hypertrophied, there is no edema, the blood pressure is not elevated, and one would never suspect a nephritis were it not for the urinary examination. Often these cases have to be differentiated from orthostatic albuminuria, which is not difficult, as in the latter condition the urine contains albumin when the patient is up and around, and does not when he is in bed; in true chronic nephritis this makes no difference. The kidney function tests in mild chronic nephritis are usually little if any diminished. The condition usually dates from a preceding acute nephritis which has not cleared up. The prognosis is uncertain. Hill believes that a certain number of cases may recover entirely after several years of albuminuria; others may develop a progressive and fatal severe type of chronic nephritis. The treatment is mainly hygienic, and strict dietary reduction is not necessary.

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21. Olwens and Moog: Deutsch. Arch. f. klin. med. **133**:5-6, 1920.
22. Hill, L. W.: J. A. M. A. **75**:596 (Aug. 28) 1920.

Treatment.—Christian [23] discusses the treatment of chronic nephritis. There are three purposes in treatment: (1) To stay the progress of the lesion; (2) to remove edema, if present to an annoying degree; (3) to prevent the formation and combat the effects of toxic substances, the result of the presence of the renal lesion. In certain cases salt restriction is effective in decreasing edema; in others it has no effect. Christian does not agree with the theory that edema is caused by swelling of colloids on account of increased acidity, and alkali therapy in his hands has been ineffectual and seems to be harmful in some cases. In the edema of nephritis diuretics almost always have little effect, and he has yet to see effective diuresis from a diuretic when the basis of the edema was a renal lesion. (Occasionally theocin seems to work well in chronic cases with edema, where there is no blood in the urine, but large amounts of albumin, with the pathologic condition known as the "large white kidney."—L. W. H.).

Notwithstanding the many deficiencies in our knowledge, we are able to do much to improve the condition of the nephritic, and probably we can retard the progress of the lesion which we cannot cure.

Dr. L. F. Barker, discussing Dr. Christian's paper, said that some diuretics, such as theobromin sodium salicylate and theocin, might injure the kidney cells, and that he never gave them for more than two or three days at a time. No diuretic other than these two is of any value. As regards control of the nephritis, prophylaxis is what we should preach most. If we keep every patient with acute tonsillitis in bed until the throat is well, if we take care of every acute infection by rest in bed, if we get rid of abscessed teeth and other focal infections before damage is done, if patients will have their family doctors examine them while they are well rather than wait until they are ill, we will accomplish more of what we desire.

According to Geyelin,[24] the treatment of nephritis may be considered under the following heads: (1) Diet; (2) fluid and salt intake; (3) general hygiene; (4) drugs.

Under the first heading we deal with the regulation of protein intake. Its purpose is twofold: (a) To relieve the kidney of overstrain, especially if there is a retention of non-protein nitrogen in the blood. (b) To alleviate hypertension and its concomitant symptoms. Protein restriction alone is often not very effective in relieving hypertension. When to protein restriction salt and fluid restriction is added, a marked lowering of blood pressure often occurs. It would seem that a combination of salt, fluid and protein restriction, together with a certain degree of underfeeding, is more effective in lowering blood pressure than is the restriction of either salt, fluid or protein alone.

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23. Christian: Southern M. J. **13**:545 (Aug.) 1920.
24. Geyelin: Prog. Med. Dec. 1920.

Protein restriction in certain forms of renal disease, when there is no nitrogen retention and when the blood pressure is not high, is often carried to unnecessary extremes. There is absolutely no evidence that red meat is any different than any other kind of meat, and the sooner this therapeutic fallacy is abandoned, the better.

The generally most successful methods of promoting diuresis when edema is present, are as follows, according to the severity of the case: (1) Salt restricted to 2 gm. per day with fluids from 1,000 to 2,500 c.c. permitted. (2) Salt restricted to 2 gm. per day, with fluids at 500 to 800 c.c. (3) Salt to 1 gm. a day or less, and fluids at 200 to 500 c.c. (4) When either of the first three methods for promoting diuresis has failed, the addition of from 5 to 10 gm. salt for a day may in certain rare instances promote a striking diuresis. This may not take place immediately, but when it does occur, it usually continues until edema has disappeared. (5) Method 2 or 3, plus diuretics of the caffein group.

"Any and all of the other so called diuretic drugs, such as potassium citrate, Basham's mixture, etc., are in my experience (Geyelin) wanting in any diuretic properties, and are not only useless in abolishing edema, but are actually harmful in some cases because of their effect on the gastro-intestinal tract. These diuretics should be abandoned, and I am sure that the belief in their therapeutic effect has been based on faulty observation in some instances, and in the other instances has been due to failure to recognize other conditions, such as salt or fluid restriction, that prevailed during the course of treatment, which directly contributed to the diuretic effect obtained."

Blood Chlorids.—According to Höst,[25] the concentration of chlorid in the blood serum is between 55 and 60 per cent. The organism rapidly excretes any surplus of salt, provided that this surplus does not exceed a certain upper limit. Chlorids and water are probably mostly excreted through the tubules, while the nitrogenous products go through the glomeruli. In most cases of acute glomerulonephritis the changes are rather diffuse in the beginning, and involve both glomeruli and tubules, later the glomeruli alone.

Chlorid retention in nephritis belongs to two categories: (1) Where the chlorid concentration of the blood is increased, the retention is mainly due to the kidneys, while the extrarenal factors are minor importance. (2) Where the chlorids of the blood are not increased, the cause is entirely or essentially extrarenal, in the capillaries or even in the tissue.

Acidosis.—Chace and Myers [26]: "All fatal cases of chronic nephritis with marked nitrogen retention show a severe acidosis, sufficient in

25. Höst: J. Lab. & Clin. Med. **5**:713, 1920.
26. Chace and Myers: J. A .M. A. **74**:641 (March 6) 1920.

many instances to be the actual cause of death. In some cases of acute nephritis and acute exacerbations of chronic nephritis the distress is apparently due to the acidosis, since the judicious use of sodium bicarbonate results in general clinical improvement. With the rise in the carbon dioxid combining power of the blood, the dyspnea and hyperpnea disappear."

Protein in the Diet.—According to Mosenthal [27] it is exceptional for a low protein diet to diminish the blood pressure or a high protein diet to raise it. The diminution of the waste products in the blood, as indicated by a lowering of the blood urea nitrogen is without effect upon the blood pressure.

Wordley [28] found that variations in the protein in the diet had no effect on the amount of protein excreted in the urine. The blood urea, however, varies considerably with the protein in the diet.

Functional Tests.—Fitz [29] gives a résumé of the various tests for kidney function. The phenolsulphonephthalein test and the nonprotein nitrogen concentration of the blood are the two tests of kidney function most in use. They are not of great value in the diagnosis of chronic nephritis as they do not point out the presence of any specific type of lesion in the kidney, and as they do not demonstrate the presence of kidney disease in the absence of common physical signs. They are of most value in prognosis.

Transfusion in Acute Nephritis.—Ramsay [30] reports a case of severe acute nephritis in a soldier, with a very low blood pressure and scanty urine secretion. His condition was very grave, and death was imminent. He was transfused, thereafter improved remarkably, and recovered. Before transfusion his blood pressure was 90 systolic, 40 diastolic. Ramsay believes the prognosis to be bad in a clinically severe case of acute nephritis if the blood pressure is low. (Such low blood pressures are probably due to suprarenal involvement, usually hemorrhage. Some years ago I reported the case of a boy with acute nephritis, who had when seen, a blood pressure of only 65. This later became so low that it could not be read, and he died.—L. W. H.).

Prognosis.—Duyvis [31] is inclined to think that the prognosis of scarlatinal nephritis is not so bad as has been thought. He examined, in 1919, thirty nephritics from an epidemic of scarlet fever which occurred at Amsterdam in 1906, and in twenty-one of these there was normal kidney function. All of the thirty were in general good condition and none had a severe nephritis.

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27. Mosenthal: Am. J. M. Sc. **160**:280, 1920.
28. Wordley: Quart. J. Med. **14**:88, 1920.
29. Fitz: Boston M. & S. J. **183**:247, 1920.
30. Ramsay: Brit. M. J. **1**:766, 1920.
31. Duyvis: Nedeilandsch. Tijdschr. v. Geneesk. **2**:1339, 1919.

Summary.—There is little new as regards nephritis. By means of the newer methods of blood, tissue and urine analysis, a good deal has been learned regarding the damages to normal functioning that occur, and it is possible to determine with some accuracy the functional capacity of the organ. The tests of function that have survived are three. The determination of residual nonprotein nitrogenous substances in the blood, the phenolsulphonephthalein test, and the two hour test (fixation of specific gravity). Ambard's coefficient had a brief vogue, but in the last two years has declined in popularity, partly because it is too complicated, and partly because so many variable factors enter into its determination that there is considerable doubt whether it is founded upon truth. As regards treatment, there has been no truly great advance since the "salt free diet" was recommended twelve or fourteen years ago. The trouble is that when nephritis occurs, the damage has already been done, and there is no direct therapy to "cure" the condition; all one can do is to adust all conditions which in any way bear on the kidney, in such a way as to spare it as much as possible; and in the acute forms to allow healing to take place under favorable conditions; in the chronic forms to reduce the work to be done by the kidney, proportional to its diminished function. We are still in the dark as regards uremia, and know little of its essential nature.

As regards children especially, in whom acute nephritis is a common disease, the most fertile and practical field in which to advance would seem to be the etiology of the condition, for once one knows etiology, prevention, possibly successful therapeutics can be considered. In acute nephritis, however, prevention is, in the present state of our knowledge, of more importance than therapeusis, for as soon as the acute nephritis has developed, we know that tissue damage has been done, and that with what we know at present, at any rate, but little can be done to cure the condition: we can simply provide satisfactory conditions for the tissue injury to heal by the force of nature, in the same way that we provide satisfactory conditions for any other tissue injury, such as a burn to heal.

We know that in children most nephritic conditions occur secondary to streptococcus or other infection elsewhere in the body, especially throat infection, but that in some cases the nephritis occurs without manifest preceding infection. If we knew the exact agent that caused the damage, if we knew whether it was active over only a short period of time, or over all the period during which the hematuria and other symptoms of nephritis persisted, then we could develop means to combat it—and until we know much more fully than we do at present, the exact occurrences that take place in the kidney at the beginning of an acute nephritis, we shall never have an adequate knowledge of it, or a therapy better than we have now.

The sequence of nephritis after acute infection elsewhere in the body is clear enough; the question is, what exact processes take place which make nephritis possible, and how can they be prevented? Do bacteria find their way into the kidney and die out as soon as the damage is done, or is it bacterial toxin, and if so, just what are the chemical relationships which cause the bacterial toxin to injure the kidney tissue. Or is it something else entirely—perhaps changes caused in the blood by infection which injure the delicate kidney tissue? If it is toxin, how long is the toxin active, and are there any means to combat it? What happens at the exact moment the kidney is damaged; is it damaged all of a sudden, or are there slower changes which take place before the visible signs of damage occur in the urine?

In childhood, we have no nephritis from slow going "wear and tear" of the kidney, such as we see so often in the adult; acute changes caused by infection or other agencies of which we know nothing bring about what we know as acute nephritis, and its sequel, chronic nephritis. Infection dominates the picture: What is urgently needed now is a closer study of the exact processes which occur in the kidney when it suffers on account of infectious processes elsewhere in the body.